2 Consultative hematology 1: hospital-based and selected outpatient topics

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The role of the hematology consultant

A hematology consultant provides expert advice about the diagnosis and management of nonmalignant or neoplastic hematologic disorders to requesting physicians and other health care providers in a broad range of scenarios. A consultation request might involve an adult general medical patient, a child or adolescent, a pregnant person, a perioperative patient, or an individual who is critically ill. Settings can be inpatient or outpatient, and the timing may be emergent, urgent, subacute, or elective. Other responsibilities might include serving on committees to maintain a formulary, standardizing use of anticoagulation, developing clinical practice guidelines, establishing policies and procedures for transfusion services, or providing a systems-based approach to an area of unmet need in a health-care system. Additionally, in the era of rising health care prices, expert consultation must also seek to be cost-effective by avoiding unwarranted diagnostic and therapeutic measures. In this effort, the American Society of Hematology (ASH) Choosing Wisely campaign seeks to identify and educate clinicians on commonly performed tests or procedures within the realm of hematology that are unnecessary, not supported by evidence, duplicative, or potentially harmful

The online version of this chapter contains educational multimedia components on normal hematopoiesis and the mechanism of action of anticoagulants.

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Off-label drug use: Jennifer R. Green and Shannon L. Carpenter: corticosteroids and rituximab for use in TTP; ATIII and activated protein C for DIC; cyclophosphamide, corticosteroids, IVIG, and rituximab for CAPS; corticosteroids, intravenous immunoglobulin, rituximab, and thrombopoietin receptor agonists for pediatric ITP; rituximab for adult ITP and TTP; granulocyte-stimulating factor outside of severe congenital neutropenia; desmopressin for use in platelet function disorders; desmopressin, recombinant FVIIa, prothrombin complex concentrate, activated prothrombin complex concentrate, fibrin glue, ε-aminocaproic acid, and tranexamic acid for use in surgical bleeding and reversal of direct oral anticoagulants; IVIG for posttransfusion purpura; IVIG for drug-induced ITP; conjugated estrogens for use in uremic bleeding; hemoglobin-based oxygen carriers for anemia in patients who refuse blood products.

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Table 2-1 Principles of effective consultation and interphysician communication

Principle	Comment
Determine the question being asked	The consultant must clearly understand the reason for the consultation
Establish the urgency of the consultation and respond in a timely manner	Urgent consultations must be seen as soon as possible (communicate any expected delays promptly); elective consultations should be seen within 24 hours
Gather primary data	Personally confirm the database; do not rely on secondhand information
Communicate as briefly as appropriate	Compliance is optimized when the consultant addresses specific questions with 5 succinct and relevant recommendations
Make specific recommendations	Identify major issues, limit the diagnostic recommendations to those most crucial, and provide specific drug doses, schedules, and treatment guidelines
Provide contingency plans	Briefly address alternative diagnoses; anticipate complications and questions
Understand the consultant's role	The attending physician has primary or ultimate responsibility; the consultant should not assume primary care or write orders without permission from the attending
Offer educational information	Provide relevant evidence-based literature or guidelines
Communicate recommendations directly to the requesting physician	Direct verbal contact (in person or by phone) optimizes compliance and minimizes confusion or error
Provide appropriate follow-up	Continue involvement and progress notes as indicated; officially sign off the case or provide outpatient follow-up

Adapted from Goldman L, Lee T, Rudd P. *Arch Intern Med*. 1983;143:1753-1755; Sears CL, Charlson ME. *Am J Med*. 1983;74:870-876; and Kitchens CS et al, Consultative Hemostasis and Thrombosis, 4th ed. (Elsevier; 2019:2-58).

(https://www.hematology.org/education/clinicians/guidelines-and-quality-care/choosing-wisely). Common to all contexts, an effective consultation requires the referring clinician and the consultant to have a clear understanding of the questions being asked, which will guide the aims and comprehensive nature of the recommendations.

A clinical hematologist must understand the principles behind successful consultation, including the extreme importance of multidisciplinary communication (Table 2-1). Hematologists should discuss cases as needed with all members of the health care team, including attending physicians, house staff, fellows, students, the patient, and their family. A commitment to optimizing communication ensures maximal compliance with recommendations and the highest quality of comprehensive patient care. This chapter discusses some of the most common consultation scenarios, including preoperative management of hematologic disorders, inpatient and outpatient consultations, and specific issues relevant to pediatric hematology.

Consultation for surgery and invasive procedures

CLINICAL CASE

A 34-year-old female with systemic lupus erythematosus (SLE) has been referred to your clinic for perioperative management of anticoagulation. She was diagnosed with antiphospholipid antibody syndrome (APLS) after experiencing a large cerebrovascular accident (CVA) 3 months ago. She is on warfarin with an international normalized ratio (INR) goal of 2.0 to 3.0. She now requires a dental extraction for an abscessed tooth refractory to medical therapy. Considering her APLS and history of CVA, you judge her thrombotic risk to be high if warfarin is interrupted. The surgery cannot be delayed due to the risk of progressive infection. The oral surgeon is concerned about the bleeding risk. You advise the surgeon and patient to continue warfarin at the current dose and prescribe an adjuvant mouthwash containing ε-aminocaproic acid to control local bleeding.

Perioperative management of antithrombotic therapy

Hematologists are often consulted to provide recommendations on temporary interruption of antithrombotics for a surgery or procedure (see video file in online edition on mechanism of action of anticoagulants). The perioperative management of antiplatelet or anticoagulant medications is based on a concurrent assessment of risk for perioperative bleeding and appraisal of risk for thromboembolism in an individual patient's scenario. These considerations are used to determine whether antithrombotics should be interrupted prior to surgery and if bridging anticoagulation should be employed. *Bridging anticoagulation* refers to the administration of a short-acting anticoagulant around the time of interruption of a long-acting antithrombotic, often in the perioperative setting. The goal of bridging is to minimize the risk of thrombosis while allowing a temporary interruption of long-acting anticoagulation.

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Assessment of risk for perioperative bleeding

Bleeding risk is related to both surgical and host factors. Surgical factors include the location and extent of the intervention, the vascularity and fibrinolytic activity of the surgical bed, the compressibility of the site and the ability to achieve surgical hemostasis, and the probability that the procedure may induce a hemostatic defect (eg, platelet dysfunction caused by cardiopulmonary bypass). Host factors include the presence of an underlying congenital or acquired hemostatic defect and use of drugs affecting hemostasis.

A focused medical history should include a detailed personal history of abnormal bleeding including prior hemostatic challenges and response to surgeries, trauma, and childbirth. Relevant history includes comorbidities or use of medications that could affect hemostasis, including nonprescription drugs and herbal supplements. Patients should be queried specifically about common procedures such as tooth extraction, tonsillectomy, and tympanostomy tube placement. Patient and family history should examine details of prior spontaneous, traumatic, or surgically induced bleeding episodes. Inquiry should include primary relatives with a history of epistaxis, bruising, postpartum hemorrhage, heavy menstrual bleeding, umbilical stump bleeding, and cerebral hemorrhage. A targeted physical examination to screen for comorbid conditions affecting hemostasis, such as liver disease, connective tissue, or vascular disorders should be performed as a complement to the history. In patients without a personal or family history suggesting a bleeding disorder, preoperative hemostatic laboratory testing is neither cost-effective nor informative. However, if the history or physical examination is suggestive of a bleeding diathesis, preoperative testing should include a platelet count, prothrombin time (PT), and activated partial thromboplastin time (aPTT). Bleeding assessment tools have been published with varying degrees of sensitivity and specificity for inherited bleeding disorders and may assist in consideration of additional testing.

Normal initial laboratory testing does not exclude a clinically important bleeding diathesis such as a platelet function defect, von Willebrand disease (VWD), mild factor deficiency, or a fibrinolytic disorder, and further testing should be guided by the clinical history and the results of the initial laboratory evaluation. Once a diagnosis has been established, a plan for perioperative hemostatic management should be developed based on the nature and severity of the defect and the bleeding risk of the anticipated procedure. Although high-level evidence is lacking, a fibrinogen of at least 100 mg/dL and a platelet count of at least 50×10^9/L is desired for moderate- to high-risk procedures. For neurosurgery and ophthalmologic procedures, it often is prudent to target a platelet count of at least 100×10^9/L.

A common preoperative hematology question is what to do with an isolated, prolonged PTT in a patient without a bleeding history. The most common cause is the presence of a lupus anticoagulant. If the lupus anticoagulant testing is positive in this scenario, then no further workup is needed prior to proceeding with surgery because the bleeding history is the best predictor of ability to tolerate invasive procedures. In those without sufficient prior hemostatic challenges or negative lupus anticoagulant testing, further evaluation of the prolonged PTT must be completed before elective surgery to exclude the possibility of a clinically relevant factor deficiency.

Assessment of risk for thromboembolism

In general, patients may be classified as having a high, moderate, or low risk of perioperative thromboembolism. Individuals with mechanical mitral valves, atrial fibrillation with CHA_2DS_2VASC scores of greater than or equal to 7, recent (within 3 months) CVA or venous thromboembolism (VTE), rheumatic valvular heart disease, or severe thrombophilia (eg, APLS, deficiencies of antithrombin, protein C, or protein S) are considered high risk. Those with atrial fibrillation with CHA_2DS_2VASC scores of 5 to 6, VTE or CVA within the last 3 to 12 months, heterozygous factor V Leiden mutation, or heterozygous factor II mutation are considered moderate risk. Patients with a remote history of VTE more than 12 months prior and without concurrent thrombotic risk factors or atrial fibrillation with CHA_2DS_2VASC scores 1 to 4 and no prior thrombotic event are classified as low risk. Individual patient factors that are not captured in this classification scheme, as well as type of surgery, should be considered in estimating an individual patient's perioperative thrombotic risk and whether bridging anticoagulation is necessary.

This thrombotic risk must be weighed against the risk of surgical hemorrhage. For example, in patients with high risk of perioperative thrombosis, continuation of warfarin rather than bridging with heparin in those requiring pacemaker or implantable cardioverter-defibrillator surgery reduces clinically significant device-pocket hematomas without any difference in thromboembolic events. An assessment of hemorrhagic risk should consider the propensity for bleeding associated with both the procedure and antithrombotic agent in question. Additional information about use of anticoagulants in the perioperative setting is found in Chapter 9.

In addition, the patient's prior history of bleeding, comorbidities that may affect bleeding (eg, renal dysfunction, malignancy, or hypertension), as well as concomitant

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use of antiplatelet or nonsteroidal anti-inflammatory medications are important in determining overall bleeding risk. Generally, procedures or surgeries associated with the potential for intracranial, intraocular, spinal, retroperitoneal, intrathoracic, or pericardial bleeding are considered high risk for bleeding. Procedures with a low bleeding risk include nonmajor procedures (lasting <45 minutes), such as general surgical procedures (hernia repair, cholecystectomy), dental, or cutaneous procedures.

An evidence-based approach to the perioperative management of patients on warfarin undergoing major surgery is shown in Figure 2-1. Temporary discontinuation of warfarin, approximately 5 days until normalization of the INR, is recommended in all patients. Bridging anticoagulation with therapeutic-dose low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) may be considered depending on the patient's risk of thromboembolism.

The BRIDGE trial randomized patients with atrial fibrillation that required warfarin interruption for a procedure or surgery to bridging anticoagulation with LMWH versus no bridging anticoagulation. The authors found that foregoing bridging anticoagulation was noninferior to perioperative bridging with LMWH for the prevention of arterial thromboembolism with the benefit of decreased major bleeding. In patients requiring minor dental procedures, warfarin may be continued with coadministration of an oral antifibrinolytic agent, if needed, or warfarin may be stopped 2 to 3 days before the procedure. Warfarin also may be continued in patients undergoing minor dermatologic procedures with the use of adjunctive local hemostatic measures as necessary. Cataract surgery also may be performed without interruption of warfarin. Perioperative anticoagulation should be used with caution after certain procedures such as prostate or kidney biopsy, where postoperative bleeding may be stimulated by the highly vascular tissue and endogenous urokinase; large colonic polypectomies that can be associated with bleeding at the stalk; and cardiac pacemaker or defibrillator implantation where a pocket hematoma may form. For intracranial or spinal surgery, bridging therapy is often not feasible. For patients or procedures thought to be at high risk for bleeding, an INR <1.5 should be achieved the day prior to surgery. If LMWH bridging is deemed necessary, then the last dose should be half the normal daily dose and administered 24 hours before the procedure to avoid residual anticoagulant effect. Depending on the patient's underlying thrombotic risk, postoperative options include waiting 48 to 72 hours after surgery before resuming full-dose LMWH bridging therapy. In the interim an intermediate or prophylactic LMWH or mechanical prophylaxis may be utilized if the bleeding risk is extremely high. For neuraxial anesthesia, the dosing and timing of perioperative LMWH follows the practice guidelines laid out from the American Society of Regional Anesthesia.

Like warfarin, the direct oral anticoagulants (DOACs) dabigatran, rivaroxaban, apixaban, and edoxaban must be discontinued before major surgery. However, unlike warfarin, the predictable, short half-life of these newer anticoagulants allows for relatively short-term cessation preoperatively, without the routine need for bridging anticoagulation. Most patients can safely undergo procedures within 24 to 48 hours of their last dose of these new oral anticoagulants, depending on surgical risk of bleeding. However, with renal

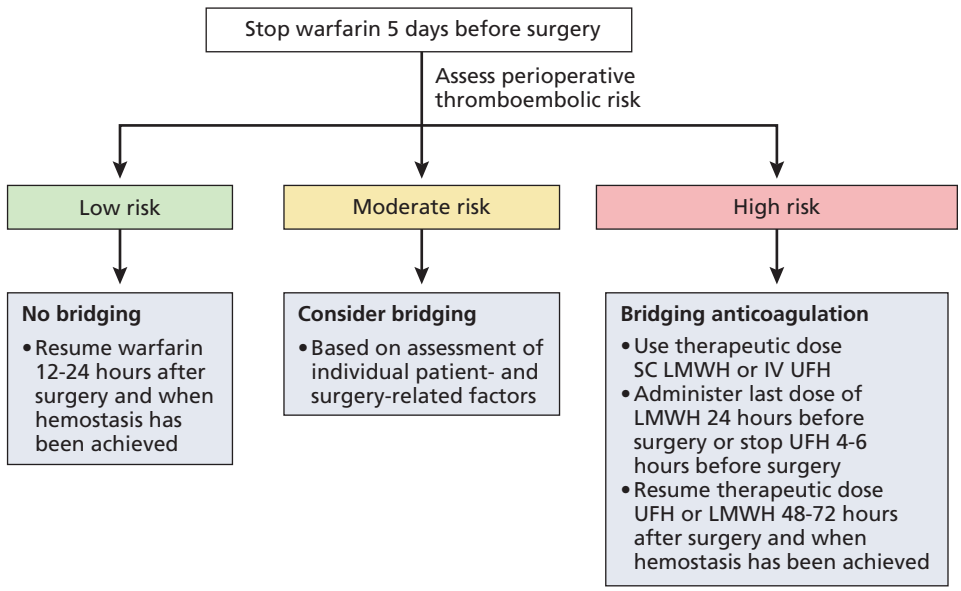

Figure 2-1 Approach to perioperative management of patients on warfarin undergoing major surgery. Management should be informed by an individualized assessment of host- and surgery-related risk factors for perioperative thromboembolism and hemorrhage, as well as patient values and preferences. IV, intravenous. Adapted from Douketis JD et al. *Chest*. 141:e326S, with permission.

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Table 2-2 Perioperative cessation and resumption of direct oral anticoagulants

	Bleeding risks of intervention for type of DOAC*			
	Dabigatran		Apixaban/edoxaban/rivaroxaban	
Creatinine clearance	Low risk	High risk	Low risk	High risk
≥80 mL/min	≥24 h	≥48 h	≥24 h	≥48 h
50-80 mL/min	≥24 h	≥72 h	≥24 h	≥48 h
30-50 mL/min	≥48 h	≥96 h	≥24 h	≥48 h
15-30 mL/min	Not indicated	Not indicated	≥36 h	≥48 h
<15 mL/min	No official indication for use		Apixaban hold time is unknown	
	There is no need for parenteral bridging with LMWH or UFH			
Resumption after procedure†	≤24 h	24-48 h	≤24 h	>48-72 h

Adapted from Heidbuchel H, Verhamme P, Alings M, et al. *Europace*. 2015;17:1467-1507, with permission from Oxford University Press (UK); © European Society of Cardiology.

*For patients on dabigatran 150 mg twice daily, apixaban 5 mg twice daily, edoxaban 60 mg once daily, or rivaroxaban 20 mg once daily.

†Depending on whether hemostasis is achieved. If significant risk for perioperative thrombosis exists, prophylactic or intermediate doses of UFH or LMWH should be considered until full therapeutic anticoagulation with a direct oral anticoagulant is resumed.

impairment, hepatic impairment, older age, and concurrent antiplatelet medications, longer cessation intervals may be necessary preoperatively (Table 2-2). Given the short onset of action of these drugs, hemostasis must be achieved postoperatively before restarting the direct oral anticoagulants. Perioperative planning on DOACs is an important consideration and a focus of clinical investigation.

A standardized interruption protocol in atrial fibrillation patients taking DOACs was evaluated in the Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) trial. This study noted low risks for both perioperative bleeding and CVAs with the adopted interruption schedule. Measurement of preoperative factor Xa levels revealed that majority of patients had residual anticoagulant levels less than 50 ng/mL prior to surgery. Further study is needed to evaluate DOACs in the perioperative setting.

Perioperative management of antiplatelet therapy, such as with oral anticoagulants, relies on an assessment of the individual patient's thrombotic risk as well as the nature of the planned procedure. In general, patients may remain on aspirin for minor dental or dermatologic procedures and cataract surgery and should be continued in patients judged to be at moderate or high risk for thrombosis in these scenarios. For major noncardiac surgery, many guidelines suggest holding aspirin for at least 7 to 10 days, though laboratory-based studies suggest aggregation response returns after 4 days without aspirin. Antiplatelet agents are typically held for intracranial, ocular, or high bleeding risk surgical procedure. Patients who require coronary artery bypass grafting may need to remain on aspirin or dual antiplatelet therapy in the perioperative setting, depending on the clinical scenario and cardiovascular risks.

In patients with a coronary stent who are receiving dual antiplatelet therapy and require surgery, it should be deferred, if possible, during the period of highest risk for in-stent thrombosis (6 weeks after placement of bare metal stents, 6 months after placement of drug-eluting stents). After this period has passed, clopidogrel or prasugrel may be suspended temporarily for surgery. If surgery cannot be delayed, dual antiplatelet therapy should be continued during and after surgery. Perioperative bleeding is a concern when continuing antiplatelet or anticoagulation medications, however a benefit and risk assessment should guide a targeted patient approach based in the individualized clinical scenario. Some available strategies and existing hemostatic products for the management of acute bleeding episodes are described in the following section.

Management of hemorrhage

Perioperative hemorrhage may be due to inadequate local hemostasis or a systemic hemostatic defect. Hemostatic defects might include an unrecognized preexisting bleeding diathesis, drugs, uremia, or disseminated intravascular coagulation (DIC). Not to be overlooked is the increased risk of bleeding induced by acid-base disturbances and hypothermia. Close attention should be paid to the pattern of bleeding, specifically the timing in relation to surgery, the location, and the tempo of the bleed. A structural defect is more likely with a single site (versus multiple sites) of bleeding, with sudden onset of bleeding (versus delayed bleeding following initial hemostasis), and/or with brisk bleeding (versus slow, persistent oozing).

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Certain surgeries are associated with specific hemostatic defects. Excessive blood loss in cardiopulmonary bypass surgery may be a secondary result of the bypass circuit on platelet function, fibrinolysis, or possibly due to antiplatelet agents, heparin, or other anticoagulants. Liver transplantation carries unique risks because of the temporary loss of coagulation factor synthesis and enhanced fibrinolysis. During reperfusion of the transplanted liver, tissue-type plasminogen activator is released into the circulation and proteolysis of von Willebrand factor (VWF) occurs.

All patients with surgical bleeding should undergo an immediate basic hemostatic laboratory evaluation, including a platelet count, PT, aPTT, and fibrinogen. Blood must be drawn from a fresh peripheral venipuncture site due to the common contamination of blood samples with heparin flushes, saline, erythrocytes, or plasma. Significant abnormalities of any of these initial parameters suggest a systemic hemostatic defect, which may require specific hemostatic therapy. Clinically significant thrombocytopenia or fibrinogen deficiency in a bleeding surgical patient mandates appropriate therapy and further testing to identify the cause of the deficiency. In general, cryoprecipitate and platelets should be transfused to maintain a fibrinogen concentration of at least 100 mg/dL and a platelet count of at least 50×10^9/L (100×10^9/L for organ- or life-threatening bleeding), respectively. Fibrinogen concentrate is available in many centers and may be used instead of cryoprecipitate. Hypothermia, hypocalcemia, and acid-base disturbances should be corrected.

Although the thromboelastograph and rotational thromboelastogram have traditionally been used more by the anesthesiologist than the hematologist, these tests can provide an accurate and rapid method of diagnosing hyperfibrinolysis, as seen in cardiopulmonary bypass and orthotopic liver transplant. There is growing interest in the utilization of global hemostasis assays to guide transfusion replacement therapy in trauma-induced coagulopathy and in surgical patients to predict thromboembolic events. For more discussion about thromboelastographs, see Chapter 12.

If basic hemostatic laboratory parameters are normal or bleeding persists after correction of these parameters, inadequate local hemostasis due to vessel injury is suggested and surgical exploration is warranted. Some systemic bleeding diatheses (eg, mild deficiency of factors VIII, IX, or XI, von Willebrand disease, qualitative platelet defects, or a disorder of fibrinolysis) may not be identified by basic laboratory testing. Patients with mild factor deficiencies may have a normal or near-normal aPTT. Clinicians should maintain a high index of suspicion for these disorders in a patient with persistent unexplained surgical bleeding and test for specific coagulation factor levels as indicated.

Adjunctive agents may be used alone for minor bleeding or as a complement to product replacement for major bleeding in selected patients and clinical circumstances. Desmopressin acetate (DDAVP) may be used for mild bleeding in disorders such as mild hemophilia A, mild von Willebrand disease, or qualitative platelet defects. However, responsiveness to DDAVP should be documented before its use in the acute setting, as some patients may exhibit a suboptimal response to DDAVP and may need a different hemostatic product. Compliance with dosing limitations of DDAVP and adherence to the weight-based fluid restrictions following administration is paramount, due to risk for hyponatremia and seizures if not observed. Topical fibrin sealants may also be used to reinforce local hemostasis.

Mucocutaneous bleeding or areas of high fibrinolysis may respond to antifibrinolytic therapy with tranexamic acid or ε-aminocaproic acid. However, tranexamic acid and ε-aminocaproic acid have also been shown to reduce blood loss and blood transfusion in patients without known bleeding disorders following cardiac surgery, liver transplantation, orthopedic surgery, and prostatectomy. An observational study of 4374 patients undergoing coronary revascularization surgery on cardiopulmonary bypass showed that use of these agents was associated with a 30% to 40% reduction in surgical blood loss without an increased risk of thromboembolism. For patients with a prior history of thrombosis, bleeding that occurs while taking a DOAC can be a common clinical scenario as well.

For most patients, holding a DOAC in the setting of mild bleeding is adequate for hemostasis given their short half-life, and antifibrinolytic agents may be used as an adjunct. For severe life-threatening bleeding, reversal with the appropriate agent may be warranted. Idarucizumab is an available reversal agent for dabigatran; andexanet alfa is approved to reverse the anticoagulant effects of rivaroxaban and apixaban. Additionally, administration of a 4-factor prothrombin complex concentrate (PCC) is commonly used in these bleeding scenarios as well; the reader is cautioned that use of 4-factor PCCs for this purpose is an off-label approach and further studies are needed.

Recombinant factor VIIa products (rFVIIa and rFVIIa) are approved in the United States for the treatment of patients 12 years and older with congenital hemophilia A or B with inhibitors. Only rFVIIa is currently approved for use in congenital factor VII deficiency, acquired hemophilias, and Glanzmann thrombasthenia with platelet refractoriness. Despite these limited indications, the majority of rFVIIa usage is off label, especially for the management of perioperative bleeding. Controlled trials have shown rFVIIa to be of no benefit in reducing

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transfusion in cirrhotic patients undergoing partial hepatectomy or orthotopic liver transplantation. Studies have highlighted the potential thrombotic risk with off-label use of rFVIIa. In a meta-analysis of 35 randomized controlled trials of rFVIIa for unapproved indications, the overall rate of thromboembolism in rFVIIa-treated subjects was 9.0%. The rate of arterial, but not venous, events was higher in subjects receiving rFVIIa, particularly among those 65 years and older. The indiscriminate use of rFVIIa for the management of perioperative hemorrhage should be discouraged; however, it may be useful for selected patients with life-threatening bleeding despite conventional measures and appropriate transfusion therapy. Advanced age and preexisting cardiovascular risk factors may increase the risk of arterial thromboembolic complications with rFVIIa.

Prothrombin complex concentrates are plasma-derived concentrates of the vitamin K–dependent clotting factors. PCCs are classified as either 3- or 4-factor depending on the amount of FVII included and were approved for treatment of hemophilia B. The 4-factor PCC Kcentra is approved for the urgent reversal of vitamin K–antagonist therapy in adult patients with major bleeding. Studies are ongoing to determine its efficacy in hemostasis for bleeding occurring on the direct oral anticoagulants. Activated PCCs contain variable amounts of activated vitamin K–dependent clotting factors and are approved for use in acute bleeding due to acquired or congenital hemophilia with inhibitor.

Prevention and treatment of postoperative venous thromboembolism

VTE is a common and potentially lethal complication of surgery. Pulmonary embolism remains a leading cause of preventable death in hospitalized patients. Despite contemporary thromboprophylaxis, postoperative VTE rates remain unacceptably high. Risk factors for VTE in surgical patients include type and extent of surgery or trauma, general anesthesia greater than 30 minutes, advanced age, cancer, personal or family history of VTE, obesity, immobility, infection, presence of a central venous catheter, pregnancy or postpartum state, and thrombophilia. Several prediction models have been developed to estimate VTE risk in surgical patients, but all have important limitations. A general risk stratification schema recommended by the American College of Chest Physicians for patients undergoing nonorthopedic surgery is shown in Table 2-3. The ACCP guidelines use 2 validated risk

Table 2-3 General VTE risk stratification for patients undergoing nonorthopedic surgery

Risk category	Risk of VTE (without prophylaxis)	Type of surgery				
		Major general, thoracic, or vascular	Gastrointestinal, urological, vascular, breast, or thyroid	Plastic and reconstructive	Other surgical populations	General thromboprophylaxis strategies
Very low	<0.5%	Rogers score <7	Caprini score 0	Caprini score 0-2	Most outpatient or same-day surgery	Early ambulation
Low	~1.5%	Rogers score 7-10	Caprini score 1-2	Caprini score 3-4	Spinal surgery for nonmalignant disease	Mechanical prophylaxis, preferably with IPC
Moderate	~3.0%	Rogers score >10	Caprini score 3-4	Caprini score 5-6	Gynecologic noncancer surgery Cardiac/thoracic surgery Spinal surgery malignant	Pharmacologic or mechanical prophylaxis
High	~6.0%	NA	Caprini score ≥5	Caprini score 7-8	Bariatric surgery Gynecologic cancer surgery Pneumonectomy Craniotomy Traumatic brain injury Spinal cord injury Other major trauma	Combination of pharmacologic and mechanical prophylaxis

Adapted from ACCP guidelines.

NA, not applicable.

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stratification models based on risk-factor point systems (Rogers score and Caprini score). These scoring systems estimate an individual's perioperative VTE risk as low, moderate, or high by assigning a point value for various patient- and procedure-related risk factors (eg, age, obesity, degree of immobility, specific comorbidities, type of surgery planned, known thrombophilia).

A strategy for thromboprophylaxis should be based on the estimated risk of VTE and bleeding and the type of surgery. Prophylactic measures include early ambulation; lower extremity intermittent pneumatic compression (IPC); graduated compression stockings; and pharmacologic prophylaxis with low dose UFH, LMWH, fondaparinux, or oral anticoagulation. In patients judged to be at high risk for bleeding, mechanical prophylaxis is favored over pharmacologic strategies unless and until bleeding risk diminishes. Inferior vena cava filter insertion for primary prevention of DVT is generally not recommended.

In the absence of a heightened bleeding risk, most adult patients undergoing major orthopedic surgery should receive pharmacologic thromboprophylaxis, which should be continued for a minimum of 10 to 14 days after major orthopedic surgery. Postoperative bleeding risk is often best estimated by the surgeon and discussion about the patient-specific prophylaxis plan must be made in collaboration with the surgical team and patient.

When VTE occurs postoperatively, the consultant may be asked for treatment recommendations. For most low-risk procedures, full anticoagulation can be initiated safely within 12 to 24 hours after surgery. Contraindications to immediate postoperative anticoagulation include active bleeding and neurosurgical or ophthalmologic procedures in which bleeding would risk permanent injury. In patients with postoperative acute deep vein thrombosis (DVT) and a contraindication to anticoagulation, insertion of a retrievable inferior vena cava filter may be required. Once it is deemed to be safe, initiation of anticoagulation and retrieval of the filter should be completed. The duration of anticoagulation after a first, uncomplicated postoperative VTE is generally 3 months. Longer treatment may be indicated for recurrent VTE and in the setting of certain hypercoagulable conditions, such as active cancer or APLS.

Consideration of organ dysfunction or other comorbidities when selecting an agent for therapeutic anticoagulation presents the clinician with a decision point which can optimize patient safety. Edoxaban and rivaroxaban are not recommended for use in Child-Pugh Class B or C cirrhosis, and apixaban is not recommended in patients with severe liver dysfunction. LMWH, fondaparinux, dabigatran, rivaroxaban, and edoxaban should be avoided in patients with renal failure. Apixaban was approved for use in end-stage renal disease (ESRD) on hemodialysis at the 5-mg twice-daily dosing based on pharmacokinetic studies, not on clinical outcomes studies. Therefore, caution is warranted as there may still be a risk for increased bleeding. Warfarin has historically been used in many patients with ESRD as well.

KEY POINTS

- Surgical bleeding risk is associated with both patient- and surgery-related factors. Patient factors include the presence of an underlying congenital or acquired hemostatic defect and use of drugs that affect hemostasis. Surgical factors include the nature and extent of the intervention, the vascularity and fibrinolytic activity of the surgical bed, the compressibility of the site, and the ability to achieve surgical hemostasis.
- A focused medical history is the most important tool to assess the risk of surgical bleeding.
- Perioperative management of patients receiving antiplatelet or anticoagulant drugs depends on the patient's risk of thromboembolism and the risk of surgical bleeding.
- The type of postoperative thromboprophylaxis required depends on the patient's risk of VTE, the type of surgery, and the patient's risk of bleeding.
- Management of acute VTE in a postoperative patient is similar to the approach in a nonsurgical patient; however, the risk of postoperative bleeding with systemic therapeutic anticoagulation must be carefully considered.

Common inpatient consultations

This section focuses on 2 common hematological consultations in hospitalized patients: thrombocytopenia and anemia.

Thrombocytopenia

Thrombocytopenia, defined as a platelet count less than 150×10^9/L, is one of the most common reasons for hematology consultation in the hospitalized patient. The main challenges in management of hospitalized patients with thrombocytopenia are to identify the underlying cause and recognize when urgent intervention is required. A traditional approach to thrombocytopenia is to classify etiologies into conditions of decreased platelet production, increased platelet destruction, or sequestration. Although this framework is comprehensive, it does not consider features related to the individual patient. Furthermore, many disorders have more than one

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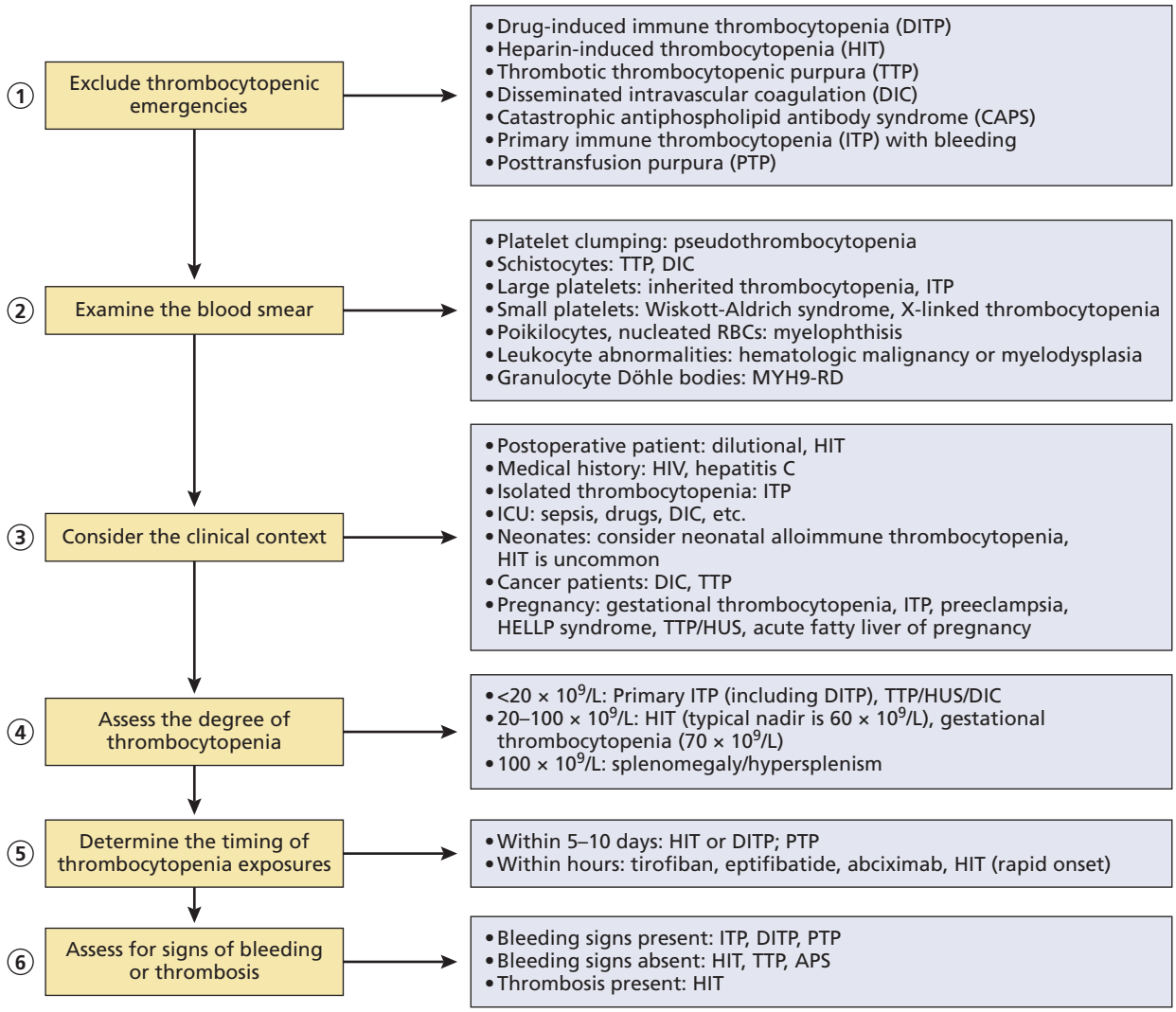
mechanism of thrombocytopenia (eg, immune thrombocytopenia [ITP] may be caused by both platelet destruction and platelet underproduction), and some critically ill patients may also have more than one cause. We propose the following practical approach to the diagnosis of thrombocytopenia in the hospitalized patient tailored to specific elements of the history, physical examination, and laboratory investigations (Figure 2-2): (1) exclude thrombocytopenic emergencies, (2) examine the blood film, (3) consider the clinical context, (4) assess the degree of thrombocytopenia, (5) establish the timing of thrombocytopenia, and (6) assess the patient for signs of bleeding and/or thrombosis.

1. Exclude thrombocytopenic emergencies

CLINICAL CASE

A 62-year-old man is in the hospital following cardiac surgery. You are consulted on postoperative day 6 because his platelet count is 30×10^9/L. His left leg is swollen, and one patch of skin around his left ankle is gangrenous. His PT, aPTT, and fibrinogen are normal. Based on the 4Ts score—a clinical prediction rule to estimate the pretest probability of heparin-induced thrombocytopenia (HIT)—you decide he has a high probability of HIT and recommend changing all anticoagulation to nonheparin products and sending specific HIT testing.

Figure 2-2 Practical approach to the patient with thrombocytopenia. Adapted from Arnold DM, Lim W. *Semin Hematol.* 2011;48:251-258, with permission.



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Any thrombocytopenic condition could become an emergency if serious bleeding occurs (eg, intracranial hemorrhage). However, some thrombocytopenic disorders are emergent diagnoses, regardless of the degree of thrombocytopenia, due to associated risks of significant morbidity and mortality without appropriate treatment. These include drug-induced immune thrombocytopenia (DITP), HIT, thrombotic thrombocytopenic purpura (TTP) or other form of thrombotic microangiopathy (TMA), DIC, catastrophic antiphospholipid antibody syndrome (CAPS), and posttransfusion purpura (PTP). These diagnoses should be considered initially for any patient with thrombocytopenia in due diligence. Consideration of the peripheral blood film and other laboratory values, clinical and medication history, and timing of thrombocytopenia can help with early recognition and treatment.

Drug-induced immune thrombocytopenia and heparin-induced thrombocytopenia

DITP is characterized by severe thrombocytopenia and may be associated with serious bleeding complications. It is usually an idiosyncratic reaction caused by drug-dependent, platelet-reactive antibodies that cause rapid platelet clearance, though other mechanisms exist as well. Expanded lists of drugs and the level of evidence for their association with thrombocytopenia have been reported (eg, https://www.ouhsc.edu/platelets/). It is important to note that over-the-counter medications and herbal medications may also be associated with DITP.

HIT is a distinct clinicopathologic syndrome associated with thrombosis rather than bleeding, and it should be considered in patients with heparin exposure who develop new onset of thrombocytopenia. HIT typically presents within 5 to 10 days of heparin contact; however, it can occur more rapidly (<1 day) in patients who may have had previous heparin exposure in the preceding 30 to 100 days. The risk of HIT is highest with unfractionated heparin and less common with LMWH.

The 4Ts probability scale can be used to assess the likelihood of having HIT. With this scale, the degree and timing of thrombocytopenia, presence of thrombosis, and possible alternative causes of thrombocytopenia are each independently considered on a scale of 0 to 2 and then summed together. A low score of 0 to 3 indicates a <1% probability of HIT, an intermediate score of 4 to 5 indicates an approximate 10% probability of HIT, whereas a high score of 6 to 8 is associated with an approximate 50% probability of HIT. The diagnosis of HIT can be confirmed with either antigen or functional assays; however, the ASH Choosing Wisely campaign recommends against testing or treating for suspected HIT in patients with a low pretest probability score. Antigen assays for anti-PF4–heparin antibodies lack specificity and may lead to false positive results in critically ill patients. Functional platelet-activation tests, such as the serotonin release assay, should be used to confirm the diagnosis.

Treatment of patients with suspected or confirmed HIT requires therapeutic anticoagulation with a non-heparin alternative. While case reports have implicated fondaparinux in the development of HIT, it has been used successfully to treat HIT in a variety of patients as well. Without proper treatment, up to 55% of patients develop thrombosis, and approximately 5% to 10% of patients die because of thrombotic complications. Management of HIT has also evolved to include use of the DOACs (dabigatran, rivaroxaban, or apixaban) as well, especially favored for use in patients who are clinically stable and at average bleeding risk. Additional information regarding this topic may be found in the 2018 ASH guidelines on management of venous thromboembolism: heparin-induced thrombocytopenia.

Thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome

TTP and hemolytic-uremic syndrome (HUS) are TMAs characterized by microangiopathic hemolytic anemia and thrombocytopenia. These disorders should be considered in any patient with anemia, thrombocytopenia, and schistocytes on peripheral blood film in the absence of another identifiable cause, such as DIC. The clinical manifestations of these disorders overlap significantly; however, patients with TTP may have neurological complications, whereas renal impairment predominates in HUS.

TTP results from either a congenital deficiency of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif), the VWF-cleaving protease, or an acquired antibody, which can be either neutralizing or nonneutralizing against ADAMTS13 activity. ADAMTS13 activity is typically <10% in patients with TTP. While testing of both ADAMTS13 levels and antibodies is available, treatment should not be withheld while awaiting results if suspicion is high due to high mortality rate if untreated. Use of the PLASMIC score can assist with stratification of patients into low (0 to 4), intermediate (5), and high (6 to 7) risk groups for suspected TTP; use of this tool improved predictive value for patients later confirmed to have severe ADAMTS13 deficiency.

With proper treatment, survival of TTP patients is 85%; however, without appropriate therapy survival drops to 10%. Management of acquired TTP requires prompt initiation of daily therapeutic plasma exchange (PLEX) with 1.0 to 1.5 plasma volumes in conjunction with

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immunosuppression, typically steroids. In patients with congenital ADAMTS13 deficiency or in those with acquired ADAMTS13 inhibition in whom PLEX cannot be initiated promptly, infusion of FFP to replace ADAMTS13 should be initiated urgently. A major responsibility of the consultant is to ensure care coordination with multiple services that are often involved in the management of TTP patients, including the intensive care unit, interventional services placing appropriate catheter access, and the blood bank to facilitate plasma exchange. Additional treatment considerations for acquired TTP include the use of rituximab and caplacizumab. An inhibitor of interaction between VWF multimers and platelets, caplacizumab showed a lower incidence of TTP-related death, recurrence of TTP, or thrombosis during treatment with caplacizumab and concurrent PLEX.

In contrast, PLEX usually does not provide benefit to patients with HUS. The most common form of HUS is associated with bloody diarrhea and is caused by enteric infection with strains of *Escherichia coli* that produce Shiga-like toxins (typical HUS or diarrhea-positive HUS). This variant accounts for up to 95% of all HUS in children, occurs in epidemics, and is generally self-limited. *Streptococcus pneumoniae*–associated HUS accounts for 5% to 15% of all childhood HUS cases and usually occurs in the setting of pneumonia, empyema, or, less commonly, with meningitis. The disease has a higher mortality and more long-term morbidity than *E. coli*–associated HUS.

The atypical form of HUS occurs without a diarrheal prodrome (diarrhea-negative HUS) and is associated with a higher incidence of ESRD and mortality. This form occurs more commonly in adults and may be caused by a dysregulation of the complement system. Mutations in genes encoding complement proteins, including factor H, membrane cofactor protein (CD46), factor I, and factors B and C3, have been described. Like TTP, management of atypical HUS often starts with empiric initiation of PLEX because of uncertainty about the diagnosis and similarity of the two presentations. Complement inhibition with the use of eculizumab or ravulizumab may improve renal function and hematologic parameters while allowing for discontinuation of PLEX once a patient is felt to have atypical HUS. Whether complement inhibitor therapy is required lifelong or may be discontinued during remission remains unclear, and this topic is under active investigation. Patients on complement inhibitor therapy should receive meningococcal vaccination at least 2 weeks prior to initiating therapy, and those who must start complement inhibitor therapy prior to this should be considered for prophylactic antibiotics.

Disseminated intravascular coagulation and sepsis

DIC occurs in critically ill patients in the setting of a serious underlying disease, such as sepsis, meningococcemia, trauma, malignancy, and pregnancy catastrophes, including placental abruption and amniotic fluid embolism. DIC also may complicate poisoning, major hemolytic transfusion reactions, and severe HIT. DIC is caused by enhanced thrombin generation because of an imbalance in the normal procoagulant and anticoagulant pathways. As a result, patients may develop significant thrombotic complications, including peripheral ischemia and skin gangrene. The clinical features are variable, and may include thrombocytopenia, increased D-dimer, and prolongation of the PT/aPTT, decreased fibrinogen concentration, and decreased protein C concentration. The peripheral blood film often shows schistocytes. A significant reduction in the level of fibrinogen may indicate early or subclinical DIC even if it does not result in fibrinogen levels below laboratory reference intervals. DIC is a dynamic process requiring repeated measurements of hemostasis and careful clinical monitoring. DIC may result in significant bleeding and may be the presenting feature of a hematologic malignancy such as acute promyelocytic leukemia. Early initiation of therapy may help arrest the coagulopathy, and mainstays of therapy may include supportive transfusion of blood products or use of fibrinogen concentrates while treating the underlying condition causing DIC. For more details, see Chapter 20.

Catastrophic antiphospholipid antibody syndrome

CAPS occurs in <1% of patients with APLS. It is a life-threatening prothrombotic condition that requires prompt recognition and management. Diagnostic criteria for CAPS are: (1) involvement of 3 or more organs, systems, or tissues; (2) development of symptoms simultaneously or in <1 week; (3) confirmation by histopathology of small vessel occlusion in at least 1 organ or tissue; and (4) laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant, anti-cardiolipin, or anti-β-2-glycoprotein 1 antibodies). A registry of patients with CAPS has provided important information on diagnosis and management. Infection is a common precipitant, but other triggers such as trauma, withdrawal of anticoagulation, and malignancy have also been described. Approximately 40% of patients with CAPS have no obvious underlying cause and mortality often exceeds 50%. A study demonstrated that up to 60% of individuals with CAPS have rare germline variants in complement regulatory genes, which may contribute

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to the development of the disease. Treatment consists of therapeutic anticoagulation in addition to aggressive therapy such as PLEX, corticosteroids, and intravenous immunoglobulin (IVIG). This multimodality approach is supported by data from the "CAPS Registry." Investigational use of complement inhibitor therapy is being evaluated in this setting as well.

Posttransfusion purpura

PTP is a syndrome characterized by severe thrombocytopenia and bleeding that develops 7 to 10 days after the transfusion of any platelet-containing blood product (such as platelet or red blood cell concentrates). It typically affects women who have had a previous pregnancy or blood transfusion and is most commonly caused by antibodies against human platelet antigen 1a (HPA-1a). The incidence of PTP is estimated at 1 to 2 per 100,000 transfusions, and it appears to be less common with leukocyte-reduced blood products. The pathophysiology remains uncertain, but may involve the formation of immune complexes, adsorption of soluble platelet antigens onto autologous platelets, or the induction of platelet autoantibodies. The process of destruction is similar to that which occurs in neonatal alloimmune thrombocytopenia, discussed later in the chapter. Diagnosis involves recognizing thrombocytopenia that occurs after transfusion of platelet-containing products and demonstrating circulating alloantibody to HPA-1a antigen in a patient whose own platelets lack this antigen. IVIG has been used to successfully treat PTP. Patients with PTP who require additional transfusions for bleeding or severe thrombocytopenia should receive HPA-1a–negative blood products if available.

2. Examine the blood film

Examination of the blood film is necessary for evaluation of thrombocytopenia. Platelet clumps suggest pseudothrombocytopenia, a clinically benign laboratory artifact caused by naturally occurring antibodies directed against the anticoagulant ethylenediaminetetraacetic acid. A repeat sample collected in citrated tube usually resolves the platelet clumping. On a smear, large platelets can indicate states of high platelet turnover, such as ITP. The blood film also allows for morphological assessment of erythrocytes and leukocytes, which may provide important clues to the underlying diagnosis: the presence of schistocytes concerns for TTP or DIC; poikilocytes or nucleated red blood cells (RBCs) may reflect a myelophthisic process; abnormal leukocytes may suggest hematologic malignancy or myelodysplasia; Döhle bodies may suggest MYH9 disorders; and toxic granulation of neutrophils may be seen in infectious processes. Hypersegmented neutrophils and macrocytosis may suggest vitamin B_{12} deficiency, lymphocytosis or circulating blasts may be consistent with a chronic or acute leukemia respectively. Dysmorphic red blood cells, hypogranulated neutrophils, or pseudo–Pelger-Huët cells may suggest myelodysplastic syndrome (MDS).

3. Consider the clinical context

The clinical context in which thrombocytopenia develops is an important clue to the underlying diagnosis. Medical history may reveal a source for thrombocytopenia such as medications, liver disease, or secondary to infections such as HIV, hepatitis C virus (HCV), or SARS-CoV-2. Thrombocytopenia is a common occurrence among critically ill patients. Age also helps narrow the differential diagnosis; for example, neonatal alloimmune thrombocytopenia (NAIT) should be suspected in any newborn with severe unexpected thrombocytopenia, and HIT is distinctly rare in children. Thrombocytopenia during pregnancy should lead to consideration of gestational thrombocytopenia, ITP, or more severe conditions such as preeclampsia; hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, or acute fatty liver of pregnancy.

Thrombocytopenia in patients admitted to the ICU

Approximately 40% of critically ill patients may have thrombocytopenia; however, the frequency varies, and most thrombocytopenia in the ICU is due to multifactorial causes. In a systematic review of medical, surgical, and mixed ICU studies, prevalent thrombocytopenia (on ICU admission) occurred in 8.8% to 67.6% of patients, and incidental thrombocytopenia (during ICU stay) occurred in 13.1% to 44.1% of patients. Thrombocytopenia was an independent risk factor for mortality. The association between thrombocytopenia and bleeding remains uncertain in this population and is likely based on additional patient factors.

HIT in the ICU

HIT is uncommon in the ICU population; however, the diagnosis and management of HIT in critically ill patients can be challenging. After major surgery, a rapid decline in platelet count beginning on days 1 to 3 is expected; in contrast, thrombocytopenia that begins between days 5 and 14, or the development of new thrombosis in an already thrombocytopenic patient, may indicate HIT. An expanded discussion on HIT can be found in the previous section and additionally in Chapter 11.

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Immune thrombocytopenic purpura

Immune thrombocytopenic purpura is characterized by isolated thrombocytopenia without other noted hematologic abnormalities and occurs in the absence of splenomegaly. Many patients with ITP have minimal bleeding. First-line therapy for adults with ITP is a course of corticosteroids; IVIG may be used if a rapid platelet count rise is needed, such as in the setting of life-threatening bleeding. Pulse dexamethasone appears to have similar efficacy to a prolonged taper of prednisone, with lower incidence of adverse events. For those failing first-line therapy with steroids, additional treatment options include rituximab, thrombopoietin receptor agonists, and splenectomy. Treatment initiation for adult ITP is recommended when the platelet count falls $<30 \times 10^9$/L or if clinically relevant bleeding occurs at higher platelet count; otherwise, clinical observation is preferred. Overall treatment goals should be aimed at reducing bleeding symptoms and improving health-related quality of life rather than targeting normal platelet counts. If possible, the 2019 ASH guidelines recommend waiting at least 1 year prior to splenectomy for refractory ITP, due to potential for remission and the thrombosis and infection risks associated with asplenia.

4. Consider the severity of thrombocytopenia

The severity of thrombocytopenia is an important clue to the diagnosis. Significant thrombocytopenia, defined as platelet counts $<20 \times 10^9$/L is typical of primary or secondary ITP, DITP, hematologic malignancies, TMAs, and DIC. HIT generally causes a median platelet count nadir of 60×10^9/L; mild thrombocytopenia can be the result of splenomegaly, primary bone marrow failure syndromes, and congenital thrombocytopenia. In patients with sepsis, platelet counts are variable, but thrombocytopenia tends to be mild or moderate. Gestational thrombocytopenia typically presents with platelet counts of greater than 70×10^9/L, which often helps distinguish it from ITP in pregnancy. Platelet counts in pregnancy less than 70×10^9warrant additional evaluation because of the differential diagnoses with risks for morbidity and mortality.

5. Establish the timing of onset of thrombocytopenia

Documentation of a normal platelet count before acute illness is helpful in narrowing the cause of thrombocytopenia. A search for exposures to drugs or blood transfusion is important. Immune-mediated platelet disorders, including classic HIT, DITP, and PTP, typically occur 5 to 10 days after exposure; however, certain drugs such as tirofiban, eptifibatide, or abciximab may cause thrombocytopenia within hours of first exposure. Rapid-onset HIT can occur after reexposure to heparin when platelet-reactive antibodies are already present and delayed-onset HIT is characterized by thrombocytopenia and thrombosis occurring several weeks after heparin exposure.

6. Assess for signs of bleeding and/or thrombosis

Typical platelet-type bleeding presents as petechiae or bruising, oral petechiae or purpura, epistaxis, and gastrointestinal, genitourinary, or intracerebral hemorrhage. Bleeding is common in patients with DITP, severe primary ITP, and in newborns with NAIT. Despite the presence of thrombocytopenia, however, bleeding is rare in HIT and TTP, because these are predominantly prothrombotic disorders, and therefore the findings of thrombosis may be more diagnostic. Diagnoses of HIT, CAPS, TMAs, or DIC should be strongly considered in patients noted to have thrombosis with concurrent acute thrombocytopenia.

Anemia

Initial evaluation of anemia in hospitalized patients

The evaluation of anemia in hospitalized patients may be challenging due to multiple confounding influences such as phlebotomy, bleeding, inflammation, medications, and the underlying processes that caused hospitalization to occur. In general, a hematologist will benefit from examining whether the anemia was present upon admission or whether acquired during the hospitalization. If present upon admission, anemia may be less likely to have resulted from inpatient confounders.

Evaluation of the mean cell volume or mean corpuscular volume (MCV) is employed to classify anemias as microcytic, normocytic, or macrocytic. This classification scheme can assist with the differential diagnosis of anemia. See Table 2-4 for additional information on this topic. Peripheral blood film review is a useful technique to evaluate for hemolytic anemias, iron deficiency, hemoglobinopathies, and other causes of anemia. Reticulocyte count is another important lab test to identify underproduction of red blood cells, which can indicate a primary bone marrow process. Increased reticulocyte count can indicate bleeding or hemolysis. For more information regarding specific types of anemia, see Chapters 6, 7, and 8.

Perioperative transfusion and ICU setting

Anemia is common in hospitalized patients, especially in the ICU and the perioperative setting. Considerable

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Table 2-4 Common differential diagnosis of anemias

Microcytic (MCV <80)	Normocytic (MCV 80-100)	Macrocytic (MCV >100)
Iron deficiency anemia	Chronic renal disease	Vitamin B_{12}, folate, or copper deficiency
Thalassemia	Hemolytic anemias	Liver disease
	Primary bone marrow processes (malignancy, aplastic anemia, bone marrow failure, etc)	Hemolytic anemias, hemorrhage, or reticulocytosis
	Multifactorial (example: combination of vitamin B_{12} and iron deficiency)	MDS, malignancies, acquired or congenital bone marrow failure syndromes
	Drug induced	Drug induced
	Anemia of chronic disease/inflammation	Alcohol abuse
	Hypothyroidism	Thyroid disorders

debate has centered on the role of RBC transfusion in critically ill and perioperative patients, largely based on the realization that transfusion may be associated with an increase in infectious risk, postoperative complications, and overall mortality. Therefore, the threshold for RBC transfusion in ICU and surgical patients has changed over time.

A landmark trial investigating the benefit of a liberal or restrictive transfusion strategy in the ICU was the Transfusion Requirements in Critical Care trial. This study suggests that RBC transfusion is generally not required for hemoglobin concentrations >7 g/dL in the ICU. The findings of a 2012 Cochrane meta-analysis show that, in general, a liberal RBC transfusion strategy (transfusion for >10 g/dL) compared with a restrictive strategy (transfusion for Hb 7 to 8 g/dL) does not improve clinical outcomes, and a restrictive transfusion strategy is as safe, if not safer. While different guidelines have recommended that transfusion is not indicated for Hb >10 g/dL, the lower threshold varies from 6 to 8 g/dL. The American Association of Blood Banks guidelines recommend that in hemodynamically stable patients without active bleeding, a transfusion threshold of 7 to 8 g/dL should be adopted. In certain high-risk populations (eg, preexisting cardiovascular disease) or those with symptoms of chest pain, orthostatic hypotension, tachycardia unresponsive to fluid resuscitation, or congestive heart failure, transfusion should be considered at hemoglobin concentrations of <8 g/dL. The Transfusion Requirements in Septic Shock trial showed that a threshold of 7 g/dL compared to 9 g/dL was as safe in patients with septic shock. In postoperative surgical patients, including those with stable cardiovascular disease, transfusion should be considered at a hemoglobin concentration of <7 to 8 g/dL. In hospitalized stable patients with acute coronary syndrome, evidence is lacking on the optimal transfusion strategy, although some experts suggest transfusion for Hb <8 g/dL and consideration of transfusion between 8 and 10 g/dL. The decision to transfuse should be based on an individualized assessment of the patient's clinical status, oxygen delivery needs, and the pace of fall in hemoglobin rather than on a predetermined hemoglobin trigger. Accordingly, the ASH Choosing Wisely campaign recommends transfusion of the smallest effective dose to relieve symptoms of anemia or to restore the patient to a safe hemoglobin range.

Refusal of blood

Not uncommonly, hematologists are asked to provide consultation for patients who refuse blood transfusions (eg, Jehovah's Witnesses). Most Jehovah's Witnesses do not accept any of the 4 major components of whole blood (red blood cells, platelets, plasma, and white blood cells), but decisions regarding individual components may vary. Whether or not one would accept blood subfractions—such as immunoglobulins, albumin, and coagulation factor concentrates—also varies between individuals. For this reason, it is vital that physicians engage Jehovah's Witnesses in shared decision making and for patients to make clear what they will or will not accept, even if death is imminent. Documentation of these wishes prior to the acute care setting can be helpful to avoid confusion or undue pressure. Treatment of anemia in this patient population is a challenge in the medical and surgical setting. Blood conservation and the use of adjunctive therapies remain the mainstay of treatment in Jehovah's Witnesses with anemia or preoperatively in anticipation of a fall in hemoglobin. Blood conservation includes minimizing daily phlebotomy for routine labs, utilizing small volume sampling with use of pediatric tubes when possible, and careful attention to minimizing blood loss intraoperatively. Supportive measures to prevent or treat anemia include swiftly stopping blood loss, stimulating erythropoiesis (eg, recombinant human erythropoietin, intravenous iron, folic acid and vitamin B_{12} supplementation), and maintaining blood volume. Transfusion decisions in a child of Jehovah's Witnesses are complicated and often benefit from consultation with an Ethics specialist.

SARS-CoV-2 infection

In 2020, the novel coronavirus SARS-CoV-2 (COVID-19) was identified as a pandemic. This disease typically presents

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with respiratory distress and increased inflammatory markers, but may present with other symptoms including fever, pain and abdominal complaints. Notable hematologic findings specific to SARS-CoV-2 infection include lymphopenia and thrombocytopenia in severely ill patients. The degree of lymphopenia may have prognostic significance. Coagulopathy is also prevalent, with elevated D-dimers also having been implicated as a mark of more severe disease. PT and aPTT may be prolonged. Fibrinogen is often low, particularly in severely ill patients.

There is an increased thrombotic risk with infection, though studies have not demonstrated a benefit to more intensive anticoagulation therapy than the prophylactic treatment currently recommended for severely ill patients requiring ICU support. However, for moderately ill patients, evidence suggests that full-dose anticoagulation may be superior. Further studies are ongoing, and ASH provides guidelines and updates at https://www.hematology.org/covid-19.

KEY POINTS

- Life-threatening causes of thrombocytopenia should be considered first in any patient presenting with thrombocytopenia: DITP, HIT, TMAs, DIC, CAPS, and PTP.
- Prompt treatment should be provided to any patient with a suggested life-threatening cause of thrombocytopenia while awaiting any definitive laboratory diagnosis.
- Examination of the peripheral blood film should be part of the investigation for any patient presenting with thrombocytopenia.
- For most patients, RBC transfusions are not required for nonbleeding critically ill patients with a hemoglobin concentration >7 g/dL or in surgical patients with a hemoglobin concentration of >8 g/dL. The decision to transfuse should be based on an individualized assessment of the patient's clinical status, oxygen delivery needs, and the rate of decline in hemoglobin rather than on a predetermined hemoglobin trigger.
- The novel coronavirus, SARS-CoV-2, presents with multiple hematologic abnormalities, and an increased thrombotic risk. Severely affected patients requiring ICU care are recommended to receive prophylactic dosage LMWH.

Common outpatient hematology consultations

This section focuses on some of the most common reasons for outpatient hematology consultations. Thrombocytopenia, leukocytosis, and leukopenia are examined in detail. Anemia is covered in other sections.

CLINICAL CASE

An otherwise healthy 12-year-old boy with a seizure disorder is referred due to thrombocytopenia. His platelet count has gradually decreased from 180×10^9/L to 38×10^9/L over the past 4 months. His only medication is valproic acid, which began 12 months ago and has been effective in seizure control. He reports no episodes of bleeding, and there are no obvious bruises or petechiae on physical examination. In conjunction with his neurologist, you recommend that he reduce the dose of valproic acid.

Mild thrombocytopenia

Patients with low platelet counts are often referred for outpatient hematology consultation. Determining the onset of the thrombocytopenia is important, which inevitably involves tracing back prior blood counts. New-onset thrombocytopenia may represent a new disease process, complication of medications, or infections. Chronic thrombocytopenia or family history of thrombocytopenia may suggest the possibility of an inherited process, such as a MYH9-related macrothrombocytopenic disorder. Other causes of thrombocytopenia include SLE, chronic underlying liver disease with or without hypersplenism, or a deficiency of nutrients required for hematopoiesis (vitamin B_{12}, folate, copper). Splenomegaly should be assessed with a physical examination and ultrasound. Human immunodeficiency virus (HIV), hepatitis B, HCV, and SARS-CoV-2 may lead to secondary immune thrombocytopenia, and these tests are reasonable to include in an upfront evaluation.

Mild thrombocytopenia in and of itself is not dangerous, but it may occur as a less severe presentation of many disorders that have other important health impacts. Thus, the patient should be questioned carefully for signs or symptoms of infection, autoimmune disease, or malignancy, including family history, and the physical examination should focus on the assessment of lymphadenopathy, hepatosplenomegaly, skin rashes, and stigmata of bleeding. As with any hematologic disorder, examination of the peripheral blood film is an essential part of the evaluation. There are no guidelines as to when or whether the bone marrow should be examined in patients with mild thrombocytopenia. The incidence of a primary bone marrow disorder such as myelodysplasia increases with age, however epidemiologic studies demonstrate that ITP is also common in elderly patients.

For patients with typical ITP (isolated thrombocytopenia without other abnormalities on the peripheral blood film or physical examination findings), bone marrow

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examination generally is not required unless refractory disease or an atypical presentation is associated. A bone marrow examination is generally indicated if unexplained symptoms arise, or other hematologic abnormalities appear. In any case of thrombocytopenia, close trending of complete blood counts (CBCs) is warranted to establish the trend and pace of the thrombocytopenia.

DITP was discussed prior in acutely ill patients but also should be considered in patients with mild thrombocytopenia. Drugs such as sulfa-containing antibiotics often cause severe thrombocytopenia, while others including the anticonvulsant drug valproic acid, may cause mild thrombocytopenia. Over-the-counter medications with attention to herbal supplements should also be considered as potential etiologies for mild thrombocytopenia.

Leukocytosis

Patients with unexplained leukocytosis are frequently referred to a hematologist because of concern about an underlying primary hematologic malignancy; however, this is not true with most patients. Most leukocytosis is reactive or secondary in etiology. For example, one common cause of unexplained leukocytosis is benign neutrophilia in cigarette smokers. Review of the peripheral blood film and a careful history and physical (H&P) examination are essential in these cases, as the differential diagnosis is very broad. Details on H&P should include specific queries regarding potential infectious sources or steroid use, as these are a common cause of leukocytosis. A new cardiac murmur might suggest bacterial endocarditis; or patients with exudative pharyngitis, splenomegaly, and lymphocytosis may have infectious mononucleosis. Dentition should be assessed for abscesses along with evaluation for skin wounds or ulcers. As the differential is broad, the clinician must often use clues from the history and labs to guide them. The cell type which is elevated leading to an increase in total leukocyte count also can provide a clue to the underlying diagnosis. Table 2-5 lists some specific causes of leukocytosis according to the predominant cell type that is elevated.

However, in some cases leukocytosis is indeed related to a primary underlying bone marrow process, and a key portion of the hematology consultant's role is to consider the risk for these conditions. A concomitant increase in hemoglobin or platelet count may reflect a myeloproliferative neoplasm. Chronic persistent lymphocytosis may be the first indication of an underlying chronic lymphocytic leukemia. If the peripheral blood film shows immature circulating forms, concurrent thrombocytosis, or a prominent basophilia, chronic myelogenous leukemia (CML) should be considered. The myeloproliferative neoplasm/myelodysplastic overlap conditions such as chronic myelomonocytic leukemia may have cytopenias with dysplastic findings in conjunction with pronounced monocytosis. Further workup for suspected primary processes typically includes a bone marrow biopsy and aspirate. Additional laboratory tests such as flow cytometry, cytogenetics, and next generation sequencing may be required to detect an abnormal malignant clone.

Leukopenia and neutropenia

Leukopenia is defined as a total leukocyte count that is 2 standard deviations below the mean. In evaluating a patient, it is important to check previous CBCs to establish rate of change in comparison with a congenital trend to assess for primary or acquired leukopenia. It can be further differentiated by the specific cell type that is affected. Leukopenia results from either decreased marrow production or from decreased circulation due to destruction, margination, or sequestration. Underlying autoimmune disorders, nutritional deficiencies, and hypersplenism can lead to acquired leukopenia. Infectious pathogens can also commonly cause leukopenia (eg hepatitis B, hepatitis C, etc. Epstein-Barr virus, HIV, SARS-CoV-2). A rheumatologic evaluation, including antinuclear antibody and rheumatoid factor, may suggest a previously undetected collagen vascular disorder or SLE. Splenomegaly in this setting may suggest Felty syndrome.

Evaluation should include review of the peripheral blood film for the presence of blasts, indicating acute leukemia, or pseudo–Pelger-Huët cells, seen in MDS. Examination of bone marrow with testing including flow cytometry may be helpful to identify a malignant clone. Next-generation sequencing (NGS) of the peripheral blood or marrow for mutations seen in MDS is a helpful adjunct in the evaluation of patients with cytopenias of unclear significance, however, morphologic findings remain key in confirming this diagnosis. Clonality identified by NGS may establish diagnoses such as idiopathic cytopenias of undetermined significance (ICUS), clonal hematopoiesis of indeterminate potential (CHIP), and clonal cytopenias of undetermined significance (CCUS). The clinical implications and risk stratifications of these conditions remain under investigation, evaluating associations with thrombosis, cardiovascular disease, and hematologic malignancies.

A careful medication history is also imperative. Many drugs, including antibiotics, anti-inflammatory drugs, and anticonvulsants can cause leukopenia. Drug-induced leukopenia can be dose related, as is the case with phenothiazines, or can be immune mediated. Cocaine or heroin (contaminated with levamisole) is an increasingly recognized cause of acquired leukopenia in otherwise healthy individuals. A

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Table 2-5 Hematology consultation for leukocytosis: etiologic considerations according to leukocyte subtype affected

Neutrophilia	Monocytosis	Eosinophilia	Lymphocytosis
Eclampsia	Pregnancy	Allergic rhinitis	Mononucleosis syndrome
Thyrotoxicosis	Tuberculosis	Asthma	Epstein-Barr virus
Hypercortisolism	Syphilis	Tissue-invasive parasite	Cytomegalovirus
Crohn disease	Endocarditis	Bronchopulmonary aspergillosis	Primary HIV
Ulcerative colitis	Sarcoidosis	Coccidioidal infection	Viral illness
Inflammatory/rheumatologic disease	Systemic lupus erythematosus	HIV	Pertussis
Sweet's syndrome	Asplenia	Immunodeficiency	*Bartonella henselae* (cat scratch disease)
Infection	Corticosteroids	Vasculitides	
Bronchiectasis	Juvenile myelomonocytic leukemia	Drug reaction	Toxoplasmosis
Occult malignancy	Chronic myelomonocytic leukemia	Adrenal insufficiency	Babesiosis
Trauma/burn		Occult malignancy	Drug reaction
Severe stress (emotional or physical)		Pulmonary syndromes	Reactive large granular lymphocytosis
Panic		Gastrointestinal syndromes	Chronic lymphocytic leukemia
Asplenia		Hypereosinophilic syndrome	Monoclonal B-cell lymphocytosis
Cigarette smoking		Eosinophilic leukemia	Postsplenectomy lymphocytosis
Tuberculosis			
Chronic hepatitis			
Hereditary neutrophilia			
Medications			
Obesity			
Corticosteroids			
β-Agonists			
Lithium			
G-CSF or GM-CSF			
Myeloproliferative neoplasm (CML, PV, ET)			

CML, chronic myelogenous leukemia; ET, essential thrombocythemia; PV, polycythemia vera.

list of causes of acquired leukopenia that affects neutrophils, lymphocytes, or both is included in Table 2-6.

Neutropenia indicates a deficiency of granulocytes, the main defense against bacterial and fungal infections. Neutropenia can arise from congenital or acquired sources and is classified as mild, moderate, or severe. Mild neutropenia includes an absolute neutrophil count (ANC) of 1 to 1.5 X 10^9/L. Moderate and severe neutropenia include ANC values of 0.5 to 1 X 10^9/L and <0.5 X 10^9/L respectively. Congenital forms typically present in childhood with recurrent infections. Patients with cyclic neutropenia typically have a 21-day periodicity associated with their nadir.

Congenital neutropenias are reviewed further in the pediatric section. Both large granular lymphocytic leukemia and hairy cell leukemia may cause acquired neutropenia and should be considered within the differential diagnosis during evaluation. Certain medications are classically associated with agranulocytosis from bone marrow suppression, including clozapine, methimazole, and trimethoprim-sulfamethoxazole. Neutropenia may also be seen with use of rituximab.

Patients with neutropenia may be asymptomatic and may not require treatment. Patients who are profoundly neutropenic may complain of fatigue or myalgias during the nadir. Treatment depends on the specific etiology.

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Table 2-6 Causes of acquired leukopenia

Infection associated
Postinfectious
Active infection
Sepsis
Viral (HIV, CMV, EBV, hepatitis A, B, C, influenza, parvovirus, SARS-CoV-2)
Bacterial (tuberculosis, tularemia, *Brucella*, typhoid)
Fungal (histoplasmosis)
Rickettsial (Rocky Mountain spotted fever, ehrlichiosis)
Parasitic (malaria, leishmaniasis)
Drug-induced (eg, sulfasalazine, NSAIDs, clozapine, cocaine/levamisole, trimethoprim-sulfamethoxazole, sulfonamides, cephalosporins, dapsone, vancomycin, phenytoin, valproate, deferiprone)
Agranulocytosis
Mild neutropenia
Autoimmune
Primary autoimmune
Secondary autoimmune (systemic lupus erythematosus, rheumatoid arthritis)
Felty syndrome
Malignancy
Acute leukemia
Myelodysplasia
Lymphoproliferative disorder
Large granular lymphocyte leukemia
Plasma cell dyscrasia
Myelophthisic process
Nutritional
Vitamin B_{12} or folate deficiency
Copper deficiency
Alcohol
Acute respiratory distress syndrome
Increased neutrophil margination (hemodialysis)
Hypersplenism
Thymoma
Immunodeficiency
Iatrogenic

EBV, Epstein-Barr virus.

Colony-stimulating factors should not be used unless there is a definitive diagnosis requiring such an intervention or if severe infection occurs in the setting of neutropenia. Basing initiation of colony-stimulating factors on absolute neutrophil count (ANC) should be used with consideration of the clinical context, with treatment generally reserved for patients with an ANC of <500, especially in the setting of an active infection or fever and in patients receiving some antineoplastic chemotherapy treatment regimens.

Lymphadenopathy

In adults, lymph nodes normally are not palpable except for the inguinal region, where small nodes up to 1.5 cm may be felt. Although superficial enlarged nodes can be palpated, deeper nodes require imaging with computed tomography (CT), positron emission tomography, or magnetic resonance imaging (MRI) for detection. Lymph node enlargement can occur in a variety of disorders, including infections, malignancy, and collagen vascular disorders (Table 2-7).

In the primary care setting, more than 98% of enlarged lymph nodes are nonmalignant, whereas 50% of patients referred to a specialist for lymphadenopathy are found to have malignant disease. A thorough exposure and travel history can reveal the source of underlying infections (eg, cat scratch and *Bartonella henselae*, undercooked meat and toxoplasmosis, tick bite and Lyme disease). Constitutional symptoms such as fevers, night sweats, and weight loss may suggest infection or malignancy. Review of the medication list may reveal a drug (eg, phenytoin) that is associated with lymphadenopathy.

On physical examination, large size, firm, fixed mobility, asymmetry, and the lack of pain are features suggestive of malignancy. The patient should be evaluated for splenomegaly as well. Additional laboratory investigations for patients with lymphadenopathy might include antinuclear antibody, rapid plasma reagin, tuberculosis skin testing, Epstein-Barr Virus, HIV, CBC, and review of the peripheral blood film. Patients with localized lymphadenopathy can be observed for a few weeks provided no other concerning features on history or physical exam exist. Tissue biopsy is required to determine the precise etiology of lymphadenopathy. If a hematologic malignancy is suspected, an excisional lymph node biopsy should be performed to preserve the tissue architecture. Fine-needle aspirations often provide a sample of tissue that is inadequate for making the diagnosis of lymphoma. Lymph node biopsy specimens should be sent for flow cytometry, cytogenetics, appropriate molecular genetic testing, and immunohistochemistry.

Castleman disease (angiofollicular lymph node hyperplasia) is a lymphoproliferative disorder characterized by polyclonal expansion of plasma cells and B and T lymphocytes and increased interleukin 6 levels leading to localized or systemic lymphadenopathy. The disease is categorized as unicentric, involving one lymph node region (typically in the

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Table 2-7 Causes of persistent unexplained lymphadenopathy

Localized	Generalized
Bacterial infection	Mononucleosis syndrome
Fungal infection	Epstein-Barr virus
Tuberculosis	Cytomegalovirus
Other mycobacterial infections	Primary HIV
Bartonella henselae (cat scratch disease)	Chronic HIV
Sarcoidosis	Other viral infections
Langerhans cell histiocytosis	Leptospirosis
Inflammatory pseudotumor	Tularemia
Progressive transformation of germinal centers	Miliary tuberculosis
Malignancy (eg, NHL, HD, CLL, metastatic carcinoma)	Brucellosis
	Lyme disease
Unicentric Castleman disease	Secondary syphilis
	Toxoplasmosis
	Histoplasmosis, coccidiomycosis, cryptococcosis
	Systemic lupus erythematosus
	Rheumatoid arthritis
	Still disease
	Rosai-Dorfman disease
	Sarcoidosis
	Langerhans cell histiocytosis
	Phenytoin
	Drug-induced serum sickness
	Multicentric Castleman disease
	Kikuchi disease
	Kawasaki disease
	Angioimmunoblastic lymphadenopathy
	Atypical lymphoproliferative process (eg, Castleman disease)
	Autoimmune lymphoproliferative syndrome
	Hemophagocytic lymphohistiocytosis
	Malignancy (eg, indolent NHL, HD, CLL, metastatic carcinoma)

CLL, chronic lymphocytic leukemia; HD, Hodgkin disease; NHL, non-Hodgkin lymphoma.

chest), or as multicentric, with generalized lymphadenopathy. Unicentric Castleman disease can be classified pathologically into hyaline vascular variant, plasmacytoid variant, and human herpesvirus 8 (HHV8)-positive Castleman disease. HHV8 encodes a viral interleukin 6–protein and has been implicated especially in patients with HIV. Unicentric disease of the hyaline vascular variant is typically treated with radiation therapy or local resection. Mixed histology, plasmacytoid variants, and multicentric disease can present with B-symptoms, organomegaly, and cytopenias. These aggressive subtypes may progress to lymphoma and require lymphoma-type treatment. Antiviral agents, such as ganciclovir, have been investigated in HIV-positive patients with HHV8-positive disease.

Splenomegaly

The normal adult spleen measures up to 13 cm in largest diameter and is not palpable. Spleen size typically is quantified by measuring splenic extension below the costal margin in centimeters, and splenic enlargement is not typically appreciated on examination unless the spleen size is increased. Physical examination may include percussive dullness in Traube's semilunar triangle bordered by the left sternal border, the costal margin, and lower border of the ninth rib. Ultrasonography can accurately determine the size of the spleen, and CT or MRI can be useful in assessing architectural changes due to infarction, infection, infiltration, or tumor. Doppler should be obtained along with ultrasound to detect any changes in splenic and portal blood flow to account for splenomegaly.

Splenomegaly occurs in patients with cirrhosis, heart failure, or splenic vein thrombosis when increased portal pressure causes venous engorgement and disruption of the normal splenic architecture. Other causes are splenic infarction, hematologic malignancies such as lymphoma, primary myelofibrosis, infection, and infiltrative disorders such as Gaucher disease. Splenomegaly can be seen in hemolysis such as hereditary spherocytosis or extramedullary hematopoiesis as in severe thalassemia. Solid tumor malignancies rarely metastasize to the spleen.

Normally, about one-third of platelets are sequestered in the spleen, where they are in equilibrium with circulating platelets; thus, splenomegaly can cause cytopenias (termed *hypersplenism*) because of increased splenic sequestration. In these instances, the apparent thrombocytopenia rarely is associated with clinical bleeding or requirements for platelet transfusion since the total platelet mass and overall platelet survival remain relatively normal. However, in chronic liver disease where patients have multiple hemostatic issues (eg, true thrombocytopenia from decreased thrombopoietin production, decreased production of coagulation factors and fibrinogen, hyperfibrinolysis, bone marrow suppression from HCV, and anatomical variceal bleeding) or require medical/surgical procedures, thrombocytopenia due to hypersplenism may contribute to the risk of bleeding.

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The initial evaluation of a patient with splenomegaly includes a detailed history and a thorough physical exam focusing on lymph nodes, spleen, and liver. Laboratory tests may include a CBC, peripheral film, liver function tests, urinalysis, HIV test, and chest x-ray. Imaging to evaluate malignancy or liver disease should be considered if the previously mentioned initial testing is unrevealing. Biopsy of affected tissues (eg, lymph nodes, liver, or bone marrow) may be pursued if the cause of splenomegaly is not obvious, as splenic biopsy/aspiration is typically not performed due to significant bleeding risk. Peripheral blood flow cytometry may show evidence of an underlying lymphoproliferative disorder, such as hairy cell leukemia or marginal zone lymphoma.

Diagnostic and therapeutic splenectomy may be indicated for patients with massive splenomegaly causing pain from infarction or recalcitrant cytopenias. Splenectomy may be indicated for patients with hereditary spherocytosis, ITP, or warm antibody–mediated hemolytic anemia. Because of the risk of rapidly progressive septicemia from encapsulated organisms, patients with surgical, functional, or congenital asplenia should be vaccinated for *Streptococcus pneumoniae, Haemophilus influenzae*, and *Neisseria meningitidis*. Prophylactic antibiotics are recommended for asplenic children under the age of 5 and should be considered for 1 to 2 years postsplenectomy in older children and adults. It is critically important that despite these prophylactic measures, asplenic individuals who develop a fever be treated promptly with therapeutic antibiotics. Splenectomy may be associated with a long-term increased risk of thrombotic events and pulmonary hypertension, particularly when performed for diseases with increased RBC turnover. In these cases, aggressive VTE prophylaxis should be administered to prevent thromboembolic complications in high-risk scenarios (eg, perioperative or peripartum states). On the peripheral blood film, Howell-Jolly bodies, nuclear remnants within RBCs, most often indicate the absence of the spleen from splenectomy or splenic hypofunction, as in sickle cell disease. After splenectomy, patients are often noted to have chronic leukocytosis and thrombocytosis long-term. Splenic artery embolization has been described in case reports as effective for managing the hematologic sequelae of portal hypertension such as thrombocytopenia. While those unable to undergo splenectomy may benefit from this approach, larger studies are needed to define efficacy and the ideal patient population prior to increasing use.

Gaucher disease is a lysosomal storage disorder caused by deficiency of glucocerebrosidase. Splenomegaly with concomitant thrombocytopenia and hepatomegaly are the most common clinical manifestations, while some forms demonstrate developmental delay or other neurologic disease. Diagnosis is by demonstrating decreased leukocyte glucocerebrosidase activity or by mutational analysis. Treatment with enzyme replacement therapy improves symptoms and quality of life.

KEY POINTS

- Most patients with stable, mild thrombocytopenia (platelets 100×10^9/L to 150×10^9/L) do not develop worsening thrombocytopenia or other autoimmune diseases.
- Thrombocytopenia caused by medications may be immune mediated or dose dependent.
- Hard, fixed, nontender, and enlarged lymph nodes may be features suggestive of malignancy.
- An excisional lymph node biopsy is better than a fine needle aspiration for making a tissue diagnosis of lymphoma.
- Patients requiring splenectomy should be vaccinated against encapsulated bacteria to reduce the risk of overwhelming infection.

Hematology consultations for pediatric patients

Pediatric consultation requires evaluation based on knowledge of developmental hematology and distinct etiologies that are not present in other patient populations. These key issues are discussed in this section.

Anemia

Following is an overview of anemia in the pediatric population. For additional information on individual conditions, refer to Chapters 5 to 8.

Newborns

Figure 2-3 illustrates the diagnostic approach to anemia in the newborn. At birth, infants are relatively polycythemic and macrocytic, reflecting fetal RBC production in the hypoxic intrauterine environment. Mean hemoglobin and hematocrit on day 1 of life for a term newborn are elevated (Table 2-8) and, therefore, a hematocrit that would be considered normal during childhood represents anemia in the newborn. Shortly after birth, erythropoietin declines, and by day 7, the reticulocyte count is 0.5%, resulting in a physiologic nadir hemoglobin concentration (10.7 ± 0.9 g/dL) at approximately 7 to 9 weeks of age. This nadir can occur earlier and be more pronounced in premature infants.

Careful assessment of the obstetrical and birth history, along with review of the family history for jaundice, anemia, splenectomy, or cholecystectomy, can assist in identifying the cause of anemia in the newborn. Physical

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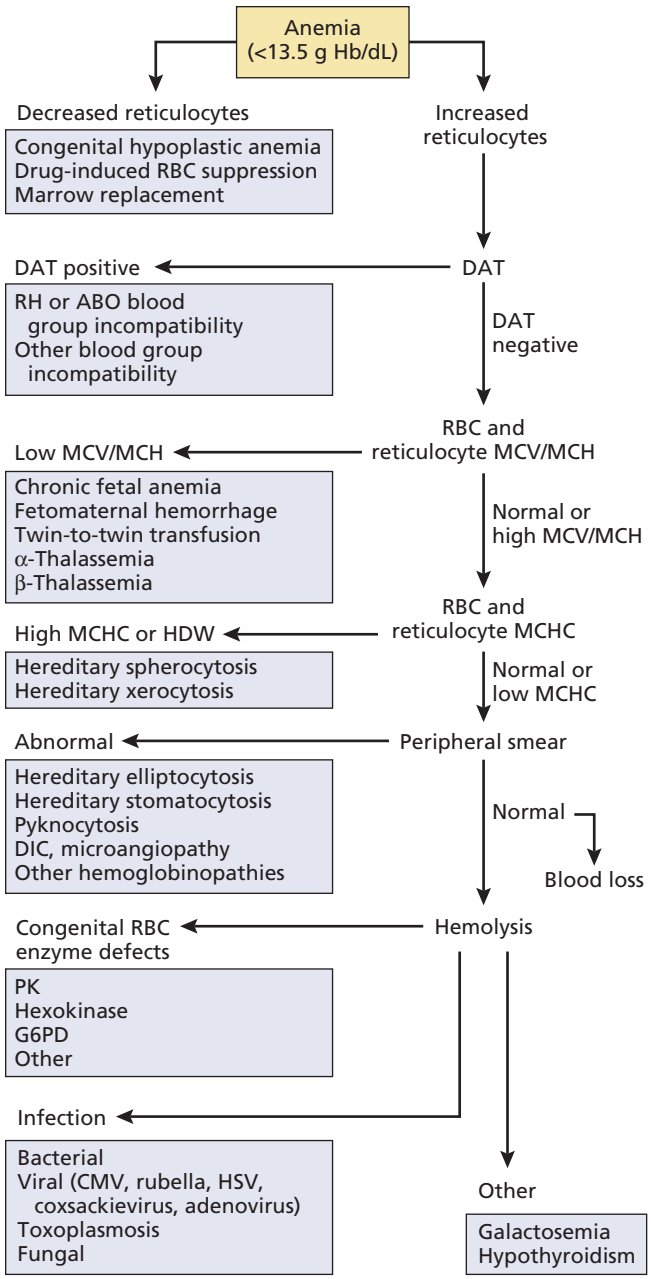

Figure 2-3 Diagnostic approach to anemia in the newborn. HDW, hemoglobin distribution width; HSV, herpes simplex virus; MCHC, mean corpuscular hemoglobin concentration; MCV/MCH, mean corpuscular volume/mean corpuscular hemoglobin; PK, pyruvate kinase. From Brugnara C et al, eds., Nathan and Oski's Hematology of Infancy and Childhood, 6th ed. (WB Saunders; 2003:19-55), with permission.

Table 2-8 Normal hematologic values for newborns

Red blood cell parameter	Term newborn day 1 ± SD*	
Hb (g/dL)	19.0 ± 2.2	
Hct (%)	61 ± 7.4	
MCV (fL)	119 ± 9.4	
Reticulocytes (%)	3.2 ± 1.4	
Coagulation/inhibitor parameter	**Healthy term newborn cord blood†**	**Healthy preterm (30-38 weeks) cord blood†**
PT (seconds)	16.7 (12-23.5)	22.6 (16-30)
INR	1.7 (0.9-2.7)	3.0 (1.5-5.0)
aPTT (seconds)	44.3 (35-52)	104.8 (76-128)
Fibrinogen (von Clauss; g/L)	1.68 (0.95-2.45)	1.35 (1.25-1.65)
Factor II activity (%)	43.5 (27-64)	27.9 (15-50)
Factor V activity (%)	89.9 (50-140)	48.9 (23-70)
Factor VII activity (%)	52.5 (28-78)	45.9 (31-62)
Factor VIII activity (%)	94.3 (38-150)	50 (27-78)
Factor IX activity (%)	31.8 (15-50)	12.3 (5-24)
Factor X activity (%)	39.6 (21-65)	28 (16-36)
Factor XI activity (%)	37.2 (13-62)	14.8 (6-26)
Factor XII activity (%)	69.8 (25-105)	25.8 (11-50)
Antithrombin III activity (%)	59.4 (42-80)	37.1 (24-55)
Protein C activity (%)	28.2 (14-42)	14.1 (8-18)
Protein C antigen (%)	32.5 (21-47)	15.9 (8-30)
Total protein S (%)	38.5 (22-55)	21.0 (15-30)
Free protein S (%)	49.3 (33-67)	27.1 (18-40)

From Reverdiau-Moalic P, Delahousse B, Body G, et al. *Blood*. 1996:88;900-906, with permission.

Hb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume.

*Adapted from Matoth Y, Zaizov R, Varsano I. *Acta Paediatr Scand*. 1971;60:317-323, with permission.

†Values are means, followed by lower and upper boundaries, including 95% of population.

examination should focus on findings such as jaundice, vital signs, and possible sources of internal blood loss. Jaundice on the first day of life is an indication of hemolysis. A review of the CBC, red cell indices, reticulocyte count, and peripheral blood film can narrow the broad differential. Additional laboratory testing should be guided by the presence or absence of findings. Newborn screening has provided an important tool for the early and asymptomatic identification of hemoglobinopathies in the United States.

Neonatal anemia can be caused by blood loss, increased RBC destruction, or decreased RBC production. Blood loss can result from placenta previa or rupture of an abnormal umbilical cord. Acute or chronic fetal-maternal hemorrhage and internal hemorrhage in the infant must also be excluded. Depending on the extent of blood loss, the infant may have signs and symptoms of circulatory shock.

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In the setting of chronic blood loss, the infant may be compensated but exhibit pallor and in severe cases congestive heart failure. Fetal-maternal hemorrhage can be confirmed, and the quantity of blood loss estimated, by the Kleihauer-Betke test on maternal blood. An uncommon source of blood loss is the twin-twin transfusion syndrome, defined as a 5 g/dL or more difference in hemoglobin concentration between twins. Hemorrhage can be acute or chronic, with variable presentations and the potential for polycythemia in the recipient twin.

Hemolytic anemia in the newborn may be either intrinsic or extrinsic. Extrinsic causes include alloimmune-mediated destruction, infection, DIC, and severe acidosis. Intrinsic causes include enzyme deficiencies, membrane defects, and hemoglobinopathies. The infant usually demonstrates a normocytic anemia with an increase in the reticulocyte count. Immune causes of anemia are becoming increasingly rare in developed countries, given the widespread use of prenatal screening and Rh-immune globulin administration to Rh-negative women. However, Rh-isoimmunization is still the most common cause of neonatal alloimmune hemolytic anemia worldwide. Immune hemolysis due to ABO incompatibility, currently the most common cause of hemolytic disease of the newborn in countries with a high human development index, is most likely in the setting of an A infant and O mother, given that maternal isohemagglutinin titers are usually higher for A than for B and that expression of the A antigen on neonatal RBCs is usually higher than expression of the B antigen. If suspected, laboratory testing includes maternal and infant red cell and Rh typing along with a direct antiglobulin test (DAT) in the infant. The peripheral blood film shows a variable number of spherocytes depending on the degree of hemolysis. A negative DAT does not exclude the diagnosis of incompatibility because A antigen density may be too low to cause cross-linking in the test. Other than Rh and ABO, anti-Kell antibodies may produce severe disease in up to 40% to 50% of affected fetuses. Common intrinsic red cell etiologies include hereditary spherocytosis and glucose-6-phosphate dehydrogenase (G6PD) deficiency, which is discussed in the following paragraphs.

Impaired RBC production is less common, but it should be considered in any infant with isolated anemia and inappropriately low reticulocyte count. Causes include congenital infections, particularly toxoplasmosis, rubella, cytomegalovirus (CMV), and herpes simplex (TORCH infections); drug-induced suppression; and, rarely, Diamond-Blackfan anemia (DBA), or other inherited disorder of red cell production.

Management requires evaluation of the possible cause and severity of the anemia, and hemodynamic status of the infant. Stable infants with mild anemia may be followed with close observation. Infants with more severe anemia can be managed with packed RBCs. Slow transfusion or exchange transfusion should be considered in infants with severe anemia and cardiovascular compromise. Specific thresholds for transfusions vary among centers and have been studied mostly in premature and low-birth-weight infants. Studies comparing restrictive (low) versus liberal (high) hemoglobin thresholds showed only minimal differences in frequency of transfusions and hemoglobin levels and did not have any impact on combined outcomes of mortality or major morbidity. In a Cochrane review of transfusion thresholds in children without respiratory support, hematocrits of 30%, 25%, and 23% were suggested as thresholds at 1, 2, and ≥3 weeks, respectively. In cases of significant anemia from blood loss, supplemental oral iron should be provided for the first several months of life. Additionally, premature infants have lower total-body iron stores than normal and should be supplemented with oral iron.

Children

Asymptomatic anemia often is discovered incidentally at approximately 12 to 15 months of age when children undergo a screening hemoglobin. This isolated value, however, does not identify the cause of anemia, and follow-up studies, including a CBC and reticulocyte count, are recommended. This section provides an overview, and details of specific diagnoses are discussed in the chapters on anemia. Classification of anemia based on red blood cell size (MCV) and reticulocyte count provides a practical approach to the child with anemia.

Microcytic anemia most often is due to iron deficiency anemia (IDA) or thalassemia. IDA is commonly diagnosed around 1 to 2 years of age. Maternal iron stores become exhausted after 6 months, and thereafter, the child must take in enough dietary iron to maintain hematopoiesis. Although the iron from breast milk is more bioavailable than that from cow's milk, it is generally inadequate as a sole source of iron beyond 4 to 6 months of life. In addition, at 1 year of life, children typically switch to iron-poor cow's milk, have inadequate intake of iron-containing foods, and develop gastrointestinal irritation with poor absorption and occult blood loss secondary to cow milk proteins. A careful diet history usually provides evidence that the child has IDA even without laboratory studies. Older children or children without an obvious dietary explanation should be evaluated for blood loss. Common sites include gastrointestinal, such as inflammatory bowel disease or celiac disease, or menstrual loss in girls. Less common are anatomic abnormalities such as a Meckel

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diverticulum or double uterus, pulmonary hemosiderosis, or Wegener granulomatosis. Other causes of microcytic anemia include lead poisoning and sideroblastic anemia. Direct and repetitive questioning and specific testing may be required to elicit the cause.

A full discussion of the laboratory evaluation for IDA can be found in Chapter 6; in children, however, additional studies are often not necessary if history, CBC, and red cell indices are highly suggestive. The best confirmatory test for IDA is response to a therapeutic trial of iron. Within 2 weeks of appropriate iron replacement (4 to 6 mg/kg/d of elemental iron), reticulocytosis and improvement of hemoglobin should be observed. The most common reasons children fail iron therapy include nonadherence, improper dosing, and a diagnosis other than IDA. If there is no response to an adequate trial of iron and parents report adherence, this treatment should be stopped and alternative causes, including blood loss and malabsorption, should be sought. Recent advances in the safety of intravenous iron makes this an option for children who require ongoing iron replacement, have poor iron absorption, or do not tolerate oral iron.

The most common alternative diagnosis is thalassemia, particularly in children of African American, Mediterranean, or Asian backgrounds. The gene deletions and corresponding nomenclature for thalassemia are discussed in Chapter 7. Review of the newborn screening result is helpful in determining α-thalassemia; however, after hemoglobin switching, 1- or 2-gene α-thalassemia is not evident on hemoglobin electrophoresis. β-thalassemia trait or intermedia may not be detected on newborn screening; however, β-thalassemia major has a hemoglobin F-only pattern. Later hemoglobin electrophoresis will reveal increased hemoglobin A_2. It is important to make the correct diagnosis so that children with thalassemia are not inappropriately treated with iron and genetic counseling can be provided. Another common and important—and often unrecognized—cause of microcytic or normocytic anemia is anemia of chronic inflammation (discussed in Chapter 6).

Common causes of normocytic anemia include: (1) early or rapid blood loss, (2) hemolytic anemia, (3) anemia of inflammation, and (4) transient erythroblastopenia of childhood (TEC). Information obtained from the history and physical may assist in the diagnosis, including onset of symptoms, recent or neonatal history of jaundice or blood loss, or family history suggestive of hemolytic anemia (jaundice, splenectomy, transfusions, and cholecystectomy). Physical examination may reveal splenomegaly and jaundice in the setting of hemolytic anemia. Vital signs can provide a clue to the duration of anemia based on hemodynamic compensation. Finally, inclusion of the reticulocyte count helps differentiate children with hemolytic anemia and a review of the peripheral blood film often provides the diagnosis.

Extrinsic causes of hemolytic anemia include immune-mediated destruction, microangiopathic destruction (DIC, TTP, and HUS covered in the previous section), and medications. Primary autoimmune hemolytic anemia can be caused by either immunoglobulin G (IgG) (warm-reactive) or immunoglobulin M (IgM) (cold-reactive) antibodies and presents with the acute onset of uncompensated anemia. While management is similar to that for adults (see Chapter 8), unlike adults, children with autoimmune hemolytic anemia have a good prognosis, with approximately 77% having an acute self-limited condition. Intrinsic causes of hemolytic anemia can be further classified by cause, including (i) enzyme deficiencies (G6PD), (ii) membrane defects (such as hereditary spherocytosis), or (iii) hemoglobinopathies (sickle cell disease). Each of these is reviewed in detail in Chapters 7 and 8. In all cases, the child usually has a normocytic anemia with an increase in the reticulocyte count; however, macrocytosis can occur in the setting of a robust reticulocyte response.

Special mention should be given to TEC, a normocytic anemia with reticulocytopenia resulting from brief disruption of normal erythropoiesis in children. Spontaneous recovery occurs with subsequent brisk reticulocyte response that often mimics acute hemolytic anemia. TEC should be suspected in an otherwise healthy child with acute onset of anemia and no abnormalities on physical examination or peripheral blood film.

Macrocytosis in childhood should always cause concern, and a bone marrow evaluation should be undertaken to look for causes of marrow failure. In early childhood, the diagnosis of DBA, a congenital pure red cell aplasia, should be considered. A quarter of patients with DBA have macrocytic anemia at birth, and 25% of children have at least one congenital anomaly, including head or face, palate, limb, or kidney abnormalities. Patients have elevated red cell adenosine deaminase activity and fetal hemoglobin levels. Bone marrow evaluation shows a normocellular bone marrow with striking paucity of erythroid precursors. Approximately 25% of DBA patients have heterozygous mutations in the ribosomal protein S19 (*RPS19*) gene, and mutations in at least 5 other ribosomal protein genes now have been identified. Treatment modalities include corticosteroids, chronic transfusions, and bone marrow transplant. Other causes of bone marrow failure should also be considered (eg, Fanconi anemia) and are covered in Chapters 16 and 19.

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Neutropenia

Newborns

Neutropenia in newborns is relatively common, secondary to the limited neonatal marrow capacity. Therefore, consumption in response to sepsis, respiratory distress, or other acute processes may exceed production. Neutropenia also may be seen in association with in-utero stress due to pregnancy-induced hypertension. In both cases, the neutropenia is transient and resolves with resolution of the underlying illness or, in the case of pregnancy-induced hypertension, within 3 to 5 days of delivery.

Neonatal alloimmune neutropenia (NAIN) results from the transplacental passage of maternal antibodies that react with paternal antigens on the infant's neutrophils. The diagnosis of NAIN generally can be made by confirming antigenic differences between maternal and paternal neutrophils, most commonly the NA1 and NA2 alleles, and by demonstrating maternal antibodies that bind to paternal neutrophils. Neutropenia can be profound, with the potential for sepsis, omphalitis, cellulitis, and other serious infections. Granulocyte colony-stimulating factor (G-CSF; 5 mg/kg/ dose) is indicated in severe cases. The condition typically resolves in weeks to months once maternal antibodies are no longer present.

NAIN must be differentiated from relatively rare inherited causes of neutropenia that are discussed in the following section. In these conditions, the neutrophil count remains severely depressed, and children are at risk for ongoing infections.

Children

Neutropenia in children is defined as an ANC $<1.5 \times 10^9$/L. It can be classified as either acquired or inherited. Acquired causes include infection, drug-induced neutropenia, and autoimmune or chronic benign neutropenia. Autoimmune neutropenia and chronic benign neutropenia of childhood likely represent a spectrum of disorders caused by immune destruction of neutrophils. The condition usually presents in children less than 3 years of age and, for the most part, is not associated with serious infections. Because of the poor sensitivity of antibody testing, a negative result does not exclude the diagnosis. Additionally, false positives may occur. Testing should be performed by an experienced lab using a panel to increase accuracy. Management is directed at treating infections with antibiotics, and G-CSF should be reserved for those patients with severe or recurrent infections associated with a low absolute neutrophil count. Prognosis is excellent, with spontaneous recovery occurring in almost all patients within 2 years of diagnosis.

A common cause of neutropenia is differences in racial neutrophil norms. Certain populations, particularly African Americans, may have lower normal limits. Usually these children have mild neutropenia (absolute neutrophils between 1.0×10^9 and 1.5×10^9/L) and no history of infection or other concerning features on physical examination, and the value is relatively stable over time. Reassurance is all that is necessary in this setting. Inherited causes of neutropenia represent a rare group of disorders, including severe congenital neutropenia (SCN), Shwachman-Diamond syndrome, and cyclic neutropenia. SCN, an autosomal recessive premalignant condition caused by mutations in the *ELA2* gene, is often diagnosed on the first day of life, and patients have persistent neutropenia associated with frequent episodes of infections. Bone marrow evaluation shows myeloid maturation arrest at the myelocyte stage. Shwachman-Diamond syndrome includes neutropenia, pancreatic exocrine insufficiency, metaphyseal chondrodysplasia, and short stature. Lastly, cyclic neutropenia is an autosomal dominant condition, usually caused by mutations in the neutrophil elastase gene, in which patients experience severe neutropenia and associated infections approximately every 21 days. Bone marrow evaluation is similar SCN during the nadir, and it may be difficult to distinguish from other causes of neutropenia at first. Careful monitoring with frequent blood counts 1 to 2 times a week for 6 to 8 weeks can help confirm the diagnosis. Treatment with G-CSF is typically considered the standard of care but may be avoided in less severely affected individuals. Less clear is the role of bone marrow transplant for those conditions that are considered premalignant.

Thrombocytopenia

Newborns

Thrombocytopenia in a neonate is defined as a platelet count $<150 \times 10^9$/L with severe thrombocytopenia generally being reserved for infants with a platelet count $<50 \times 10^9$/L. As with neutropenia, limited capacity of the neonatal marrow to increase platelet production in the face of rapid consumption can result in thrombocytopenia in the sick newborn with estimates of almost 25% of neonates in the neonatal ICU experiencing thrombocytopenia, which can be classified as early or late. Within the first 72 hours, thrombocytopenia is usually the result of antenatal or perinatal events such as perinatal asphyxia, intrauterine growth restriction, maternal hypertension, intrauterine infection, and intrauterine viral infections. It may also result from immune destruction. After 72 hours, thrombocytopenia is more likely due to postnatal events, including necrotizing enterocolitis and late onset sepsis.

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In an otherwise well infant, immune thrombocytopenia should be investigated. Knowledge of maternal medical history and platelet count is critical because management varies depending on suspicion of alloimmune versus autoimmune thrombocytopenia. Autoimmune thrombocytopenia, either primary or secondary, presents early in infancy because of transplacental passage of maternal platelet-reactive IgG (secondary to either ITP or SLE), which binds to common antigens on the infant's platelets. The mother may or may not have thrombocytopenia, as even a remote history of resolved ITP in the mother can lead to transfer of antibodies to the infant. The risk of bleeding is low, and infants often can be managed with observation alone without need for treatment. If the infant does require treatment, then IVIG can be given. Primary ITP in a child generally does not occur earlier than 6 months of age.

NAIT should be suspected in an infant born with severe thrombocytopenia, especially if maternal history is negative and maternal platelet count is normal. NAIT results from the transplacental passage of maternal antibodies that are reactive against paternal-derived antigens expressed on the infant's platelets. This condition is analogous to Rh disease, in that the mother lacks the antigen and the infant inherits the antigen from the father. Unlike Rh disease, however, first pregnancies may be affected by NAIT. The majority of NAIT cases (80%) arise because of a maternal antibody against HPA-1a. Other antigens, including HPA-5b and HPA-3b, are less common. Thrombocytopenia caused by NAIT is associated with a high risk of intracranial hemorrhage (10% to 20%); therefore, NAIT should be suspected in any healthy infant with severe thrombocytopenia and prompt management should be initiated. All infants with NAIT should be investigated for intracranial hemorrhage with either ultrasound or CT scan. Treatment is recommended for a platelet count $<30 \times 10^9$/L or $<100 \times 10^9$/L in infants with severe hemorrhage. Optimal treatment includes transfusion of HPA-compatible platelets from an antigen-negative donor. Random donor platelets should be given if antigen-negative platelets are unavailable since platelet count increments have been documented with this approach. IVIG (1.0 g/kg/d for 1 to 3 days depending on response) and methylprednisolone also may decrease the rate of platelet destruction and can be used as adjunctive therapy. Regardless of treatment, NAIT usually resolves within 2 to 4 weeks. Specific testing for NAIT, including platelet antigen typing and antibody identification, can confirm the diagnosis; however, treatment should be instituted even if results of testing are unavailable. NAIT testing is important because of the implications for subsequent pregnancies where the risk of severe thrombocytopenia is higher and can occur as early as the second trimester. Prenatal management, risk stratification, and counseling of female family members is recommended and should be undertaken in conjunction with a high-risk obstetrician.

Outside of NAIT, which carries a high risk for bleeding, the role of prophylactic platelet transfusions and desired thresholds for transfusion to prevent bleeding remain unclear. The majority of studies that have been conducted in this area have assessed platelet count, not bleeding events, as the primary outcome, making conclusions about true clinical utility difficult to draw. In one randomized trial, there was no reported increased risk for intraventricular or periventricular hemorrhage in neonates with moderate thrombocytopenia, defined as a platelet count of 50×10^9 to 150×10^9/L. Further studies are needed in this area to determine best practice.

Children

Causes of childhood thrombocytopenia generally are due to either platelet destruction or impaired platelet production. The most common cause of isolated thrombocytopenia is ITP, which can be either primary or secondary in children. Specific features of ITP in children are outlined here.

ITP is a diagnosis of exclusion based on findings of isolated thrombocytopenia in an otherwise healthy child without abnormalities on physical examination or laboratory studies, including detailed evaluation of the peripheral blood film. A bone marrow examination is not considered necessary for the diagnosis of ITP.

ASH-published guidelines recommend that children with no or mild bleeding do not require treatment regardless of the platelet count. This is based on evidence that the majority of children experience spontaneous recovery of their platelet count, treatment is unlikely to alter the course of the disease, and severe hemorrhage is a rare event even in children with severe thrombocytopenia. In addition to bleeding symptoms, physicians need to consider quality of life, access to care, and child behavior when determining therapy. When drug therapy is indicated, prospective randomized studies have demonstrated that IVIG and anti-D (in Rh-positive patients) lead to the most rapid increase in platelet count. Although anti-D is easier to administer, it has been associated with fatal intravascular hemolysis and DIC, which led to a black box warning by the US Food and Drug Administration. Short courses of corticosteroids are effective and much less costly, but they take longer to increase the platelet count. Long courses of corticosteroids are not recommended in children.

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In contrast to adult ITP, most children have an acute course with 75% of patients achieving a complete remission by 6 months from presentation. For patients with persistent or chronic disease, treatment options include intermittent use of medications, splenectomy, or modalities such as rituximab, high-dose dexamethasone, and thrombopoietin receptor agonists. The benefit of splenectomy is a high rate of durable remission, which occurs in approximately 75% of patients; however, this must be weighed against the risks associated with surgery, a lifelong risk of sepsis, and possible risk of thrombosis. Rituximab and high-dose dexamethasone have been used in children with chronic ITP to avoid or delay splenectomy, with complete remission rates of approximately 20% to 30%; however, remission duration is generally shorter than with splenectomy. Thrombopoietin receptor agonists are FDA approved for the treatment of ITP in children, most commonly for chronic disease. Studies are currently ongoing using these medications as frontline agents.

Additional causes of thrombocytopenia in children due to destruction include microangiopathic conditions and HIT (rare in children), both discussed in the adult section. Autoimmune lymphoproliferative syndrome results from impaired *fas* ligand–mediated apoptosis. Patients experience recurrent lymphadenopathy, organomegaly, and immune cytopenias. Kasabach-Merritt phenomenon is characterized by thrombocytopenia and microangiopathic hemolytic anemia associated with the vascular tumors Kaposiform hemangioendothelioma and tufted angioma, and usually presents in early childhood. Patients can develop a severe life-threatening consumptive coagulopathy, and many treatment modalities have been described, including corticosteroids, vincristine, and sirolimus.

Causes of decreased platelet production include aplastic anemia, MDS, bone marrow infiltration, and inherited thrombocytopenias. The inherited thrombocytopenias represent a diverse group of disorders (see Chapter 11). In all cases, a detailed review of the family history, physical examination looking for additional anomalies, and evaluation of platelet and white cell morphology on the peripheral blood film provide important diagnostic clues. Microthrombocytopenia in males should raise the concern for Wiskott-Aldrich syndrome or X-linked thrombocytopenia, caused by a mutation in the *WAS* gene. Wiskott-Aldrich syndrome, unlike X-linked thrombocytopenia, is associated with immune deficiency, and patients require early identification and management in coordination with an immunologist. Several conditions are characterized by macrothrombocytopenia: *MYH9*-related disease (autosomal dominant), Bernard-Soulier syndrome (autosomal recessive), *GATA1* mutations (X-linked recessive), and gray platelet syndrome (variable inheritance). Normocytic thrombocytopenia is seen in congenital amegakaryocytic thrombocytopenia (autosomal recessive), thrombocytopenia with absent radii (variable inheritance), and thrombocytopenia with radioulnar synostosis (autosomal dominant). Unlike other inherited thrombocytopenias, infants with thrombocytopenia-absent radius syndrome can demonstrate spontaneous resolution of thrombocytopenia during childhood. Although supportive care with platelet transfusions commonly is used as initial management for patients with inherited thrombocytopenia, accurate diagnosis is important because some conditions are associated with an increased risk of leukemia, and some may benefit from bone marrow transplant.

Coagulopathy

Newborns

Accurate assessment of hemostasis in the newborn requires knowledge of the normal range for coagulation parameters (Table 2-8). The vitamin K–dependent factors II, VII, IX, and X and contact factors are physiologically low in neonates, despite the routine administration of vitamin K. Notably, the normal newborn range for factor IX activity, 15% to 50%, occasionally has led to the misdiagnosis of mild hemophilia B. By contrast, several factors are at adult levels at birth, including factors VIII, V, and XIII; fibrinogen; and VWF. Because of these physiologic differences, both the median and upper limit of PT (median, 16.7 seconds; upper limit, 23.5 seconds) and aPTT (median, 44.3 seconds; upper limit, 52 seconds) are higher than ranges established for adult patients. Coagulation factor production gradually increases over the first few months of life, reaching adult levels by approximately 6 months of age. Therefore, comparison of obtained values to age-appropriate normal values is a critical first step in evaluation of a neonate with suspected coagulopathy.

In sick neonates, coagulation abnormalities can result from sepsis, asphyxia, or other triggers of DIC. Unexpected bleeding in an otherwise well newborn, such as hemorrhage at circumcision, prolonged oozing from heel stick blood draws, umbilical cord bleeding, or more bleeding or bruising than expected from a difficult delivery, should raise the possibility of an inherited bleeding disorder. Screening can be undertaken for PT and aPTT, with specific factor levels based on results and clinical concern.

The most common inherited causes of an isolated aPTT in an otherwise healthy infant are factor VIII and factor IX deficiencies, with factor XI deficiency being significantly less common. Family history may be

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suggestive of a bleeding disorder with X-linked inheritance; however, a negative family history does not exclude the diagnoses, as approximately one-third of infants represent spontaneous mutations. Although also sometimes associated with an elevated aPTT, von Willebrand disease rarely results in bleeding in the newborn unless it is severe (type 3). If there is an immediate need for treatment and the specific factor deficiency is unknown, FFP provides adequate hemostatic coverage; however, it is important to draw a sample for specific factor testing prior to administration of FFP.

Isolated elevation of the PT should prompt investigation into vitamin K deficiency. Although all infants born in the hospital should receive supplemental vitamin K, home deliveries and parental desire to avoid medical interventions have increased the incidence of vitamin K deficiency in breastfed infants. Vitamin K deficiency may be classified as early (within the first 24 hours of life), classic (between days of life 2 through 7), or late (beyond day 8 of life and as late as 6 months). Late deficiency is associated with a higher rate of intracranial hemorrhage. Infants often present with diffuse severe hemorrhage that can be intracranial, gastrointestinal, umbilical, head or neck, at injection sites, or from circumcision. Treatment for infants with mild bleeding is administration of 1 to 2 mg of vitamin K given either subcutaneously, intramuscularly, or as slow intravenous infusion. Rapid reversal of the coagulopathy begins within an hour of administration, but FFP or a prothrombin complex concentrate should be given to infants with severe bleeding. If vitamin K deficiency is severe, both the PT and aPTT will be prolonged. Additional defects that affect global hemostasis include DIC and liver disease. Alternative causes of prolongation of both the PT and aPTT include rare deficiencies in factors of the common pathway, such as afibrinogenemia or dysfibrinogenemia, prothrombin deficiency, and factor V and factor X deficiencies.

If there is a high suspicion of a bleeding disorder, and both the PT and aPTT are normal, factor XIII deficiency should be considered. This condition is an autosomal recessive disorder caused by an inability to cross-link fibrin and commonly presents with umbilical cord bleeding. A factor XIII activity is used to confirm the diagnosis. As mentioned previously, VWD variably presents with a prolonged aPTT, and cannot be excluded with normal screening labs. However, most VWD does not present with bleeding in the neonatal time period, and the most severe is typically accompanied by low factor VIII and therefore a prolonged aPTT. An additional concern in a bleeding patient with normal screening labs would be a rare platelet function defect, such as Glanzmann thrombasthenia.

Children

The diagnostic workup for a child with a suspected coagulopathy begins with a thorough history and screening with a complete blood count, PT, and aPTT. Specific considerations for additional testing depend on concerns identified on history and screening laboratory examination. Samples should be drawn from a peripheral venipuncture to avoid contamination from heparin. Here we provide an overview to guide the initial evaluation based on laboratory findings, with more specific information on individual disorders of coagulation in Chapter 10.

If an abnormality is identified, laboratory error or heparin contamination should be considered and eliminated as a possible cause. A lupus anticoagulant should be ruled out as described in the previous section on perioperative bleeding. Patients with a concerning history should be evaluated for a factor deficiency. The child may have a remote history of bleeding, such as hemorrhage with circumcision, hematomas with immunizations, swelling to extremities with mild trauma, or previous bleeding with minor procedures. Family history may provide information to guide testing, with factor VIII and IX deficiency having an X-linked inheritance. Testing for factor VIII and factor IX deficiency as well as VWD should be considered in children with a prolonged aPTT. Factor XI deficiency can also result in a prolonged aPTT and should be tested if no other abnormalities are identified. Mild hemophilia and VWD may not result in a prolonged aPTT. Therefore, specific factor testing should be undertaken if a high clinical suspicion exists.

An isolated prolonged PT usually represents a deficiency of factor VII. Inherited factor VII deficiency is a rare autosomal bleeding disorder with variable presentation and little correlation between bleeding rates and factor level. Beyond congenital factor VII deficiency, consideration should be given to acquired causes of factor VII deficiency such as liver disease and vitamin K deficiency from malabsorption, cystic fibrosis, or medication use. Given the extremely short half-life of factor VII, the PT may prolong before the aPTT in these conditions.

Prolongation of both the PT and aPTT is seen in either common pathway factor deficiencies or in the setting of multiple factor abnormalities. Common pathway factor deficiencies are rare and include deficiencies of fibrinogen, prothrombin, factor V, and factor X. More commonly, this scenario is seen with multiple factor deficiencies in the setting of liver disease, vitamin K deficiency, and DIC. Testing of a combination of factors, such as factors VIII, V, and II, often can provide information to distinguish these etiologies if they are not clinically apparent. In DIC, all 3

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are decreased; in liver disease, factor VIII remains normal or elevated; and in vitamin K deficiency, only factor II is decreased.

In all cases, treatment should be aimed at reducing hemorrhage and correcting coagulopathy with management of the underlying disease and replacement of deficient factors. If the precise deficiency is identified, specific factor replacement should be provided; however, if a specific factor is not available, the deficiency is not known, or multiple factors are involved, then FFP can be given.

Thrombosis

Newborns

Similar to pregnancy, the balance between hemostasis and fibrinolysis is shifted toward thrombosis in the newborn, with antithrombin III (ATIII) levels being mildly lower in neonates and the vitamin K–dependent anticoagulants, proteins C and S, strikingly lower (Table 2-8). Although evidence suggests that the fibrinolytic system is activated at birth, plasminogen levels are relatively low, so plasmin generation is somewhat decreased in response to thrombolytic agents. When added to the physiologic stresses of labor and delivery, the newborn period thus represents the greatest risk of thrombosis, especially in the sick neonate. Neonatal thrombotic complications include those associated with umbilical venous or arterial catheters, renal vein thrombosis, arterial and venous stroke, and cerebral sinus venous thrombosis. Clinically, it may be difficult to determine whether the thrombotic event occurred pre- or postnatally.

Screening for inherited thrombophilia in a neonate with a first thrombotic event is controversial; although some recommend screening all such infants, others conclude that unless it will alter acute management, screening is not cost effective. In addition, in neonates, age-related variation in normal factor levels may complicate interpretation of results. Lastly, in some cases, the mother and/or infant may be screened for antiphospholipid antibodies, which can cross the placenta.

Special mention should be made of the rare but potentially devastating homozygous deficiencies of protein C and protein S. Infants classically present with purpura fulminans lesions at birth without an obvious other cause for DIC. The level of protein C or S in such patients is often undetectable. There have also been reports of compound heterozygous cases. Genetic testing can be performed to confirm a congenital cause but should not delay immediate treatment with FFP, along with anticoagulation with LMWH or UFH. Anticoagulation can be transitioned to warfarin once therapeutic levels of LMWH or UFH are achieved. Protein C concentrates are approved for use in patients who have confirmed severe protein C deficiency. Generally, protein C or protein S replacement should be administered for 6 to 8 weeks, until all lesions have healed and a therapeutic INR has been achieved.

Beyond protein C and protein S deficiency, treatment in infants with acute thrombosis can include thrombolytic therapy, UFH, warfarin, LMWH, and direct thrombin inhibitors. Thrombolytic therapy can be considered in the newborn when thrombosis poses risk to life, limb, or organ function. Dosing of tissue plasminogen activator may be somewhat higher in newborns compared with dosing in older patients because of lower levels of plasminogen. UFH use may be complicated by low levels of ATIII in infants. Therefore, if it is difficult to achieve a therapeutic aPTT, ATIII levels can be checked and a supplement given if levels are low. Warfarin dosing in infants can be complicated by several factors, including changing levels of coagulation proteins in the first months of life, disparate levels of vitamin K in breast milk and fortified formulas, and lack of a liquid warfarin preparation. For these reasons, LMWH increasingly is preferred. Newborns have rapid metabolism of LMWH and thus higher starting doses are recommended in this population, and dose adjustments should be made as needed to maintain anti-Xa activity levels of 0.5 to 1 U/mL 4 to 6 hours after administration.

Children

Recent evidence suggests that thrombosis in children is becoming a more common event, perhaps because of the increased use of central venous catheters, greater recognition, or improved imaging techniques. For the most part, children with thrombosis have an identifiable secondary cause such as infection or central venous catheter, and spontaneous thrombosis is less common. Testing for thrombophilia in children with thrombosis or family history of it remains controversial; however, testing is generally recommended for children with spontaneous thrombosis. There are insufficient data to guide recommendations for routine testing in children with an acquired risk factor such as a central catheter. If desired, comprehensive testing includes protein C, protein S, and ATIII levels along with factor V Leiden and prothrombin G20210A gene mutations. Additionally, one should consider lupus anticoagulant and antiphospholipid antibody testing in a child without other causes for spontaneous thrombosis. The rationale for testing is based on the notion that identification of thrombophilia may alter duration of anticoagulation therapy and predict risk for recurrence. Treatment for children with thrombosis is similar to adults, and duration is based on the site and cause of thrombosis (see Chapter 9).

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Given that spontaneous thrombosis is rare in children, when it does occur, specific consideration should be given to anatomical causes. May-Thurner syndrome caused by pressure on the left common iliac vein by an overlying right common iliac artery should be suspected in cases of left iliac vein thrombosis and evaluated with an MRI once acute obstruction has resolved. Paget-Schroetter syndrome results from upper venous obstruction seen with thoracic outlet syndrome. Patients may report activity that requires frequent movement that raises the arm above the head leading to repeat compression. If present, proper management of both conditions involves consultation with a vascular surgeon or interventional radiology.

KEY POINTS

- Attention must be given to age-appropriate normal values when performing a pediatric consult.
- The sick newborn is particularly at risk for developing cytopenias secondary to poor bone marrow reserve in the setting of stress.
- Ideal prophylactic transfusion thresholds for red cell and platelet transfusions in neonates and children remain unknown.
- During the newborn period, antigenic differences between the mother and the infant can result in alloimmune cytopenias.
- The majority of hematologic conditions during childhood represent benign self-limited conditions and inherited causes are rare.
- ITP in children, unlike in adults, usually is acute, and management with observation alone is appropriate only for children with ITP and cutaneous manifestations.

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